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Basic Science

Immunohistochemical Expression of TGF-B1, SMAD4, SMAD7, TGFβRII and CD68-Positive TAM Densities in Papillary Thyroid Cancer

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Keywords: Thyroid cancer; TGF-β pathway; Immunohistochemical expression; Macrophages; Tumorigenesis

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Abstract

BACKGROUND: Papillary thyroid carcinoma (PTC) accounts for 80% of the thyroid malignancies that are characterised by slow growth and an excellent prognosis. Over-expression of SMAD4 protein restores TGF-β signalling, determines a strong increase in anti-proliferative effect and reduces invasive potential of tumour cells expressing it.

AIM: The study aimed to analyse the immunohistochemical expression of TGF-β1 and its downstream phosphorylated SMAD4, element and of the inhibitory SMAD7 PTC variants and their association with the localisation of TAMs within the tumour microenvironment.

METHODS: For this retrospective study we investigated 69 patients immunohistochemistry with antibodies against TGF-β, TGF – β-RII, SMAD4, SMAD7, CD68+ macrophages.

RESULTS: Patients with low infiltration with CD68+ cells in tumour stroma has significantly shorter survival (median of 129.267 months) compared to those with high CD68+ cells infiltration ($p = 0.034$). From the analysis of CD68+ cells in tumour border and tumour stroma correlated with expression of TGF-β1 / SMAD proteins, we observed that the positive expression of TGF-β1 in tumour cytoplasm, significantly correlated with increased number of CD68+ cells in tumour border ($X^2 = 5,945$; $p = 0.015$).

CONCLUSION: TGF-β enhances motility and stimulates recruitment of monocytes, macrophages and other immune cells while directly inhibiting their anti-tumour effector functions.

Introduction

The transforming growth factor beta (TGF-β) impact on the immune system and tumour progression has been studied in general and in the development of thyroid cancer [1] [2] [3] [4] [5]. TGF-β activation is induced by several mechanisms including the expression of αvβ6 integrin, chymase, elastase, MMP9 etc. [6] [7] [8]. Activated TGF-β, after binding the TGF-β receptor II (TGF-RII) efficiently trans - activates TGF-β receptor I (TGF-RI) and directly promotes tyrosine phosphorylation [9]. Then TGF-β signalling activates R-Smads (SMAD2 and SMAD3 localised in the cytoplasm), through phosphorylation and after that allows the assembly of complexes with SMAD4. These complexes re-localise to the nucleus where they can regulate gene transcription [10]. This is the active TGF–β/SMAD–dependent pathway [2]. On the opposite, SMAD7 antagonises TGF–β/Smad – dependent signalling, and induces TGF-β receptor degradation and thus preventing SMAD2 and SMAD3 phosphorylation**.** SMAD7 leads a loss of TGF–β/SMAD-dependent pathway growth inhibition [10].

Normally and in the early phase of cancer TGF–β/SMAD-dependent pathway signalling inhibits

epithelial or cancer cell proliferation, and sometimes migration and invasiveness. These processes are studied in some cases with papillary thyroid cancer (PTC) [2] [11].

In late phases tumour cells overcome TGF-β-induced suppressor effects on cell proliferation, an on the other hand tumour cells themselves may respond to this cytokine including other effects that contribute to tumour progression such as epithelial-mesenchymal transition (EMT), invasion and metastases [1] [3]. TGF-β modulates the immune response that shields a tumour from immune surveillance [12] [13].

PTC accounts for 80 % of the thyroid malignancies that are characterised by slow growth and an excellent prognosis. However, 10–15 % of cases exhibit aggressive behaviour with hallmarks of local invasion, distant metastases, treatment resistance, and motility [14] [15].

TGF-β1 normally expressed and secreted by normal thyrocytes is a potent inhibitor of thyroid cell growth [16] [17]. In tumours, TGF-β expression has been detected in 52-100% of PTC cases [18]. SMAD4 is found to be expressed in 75% of PTC cases [11] [19] and every PTC cell line [19]. **The** SMAD7 expression has been detected in 80% of PTCs and PTC cell lines [11] [20**].** It has been found that TGFβRII mRNA transcripts are mainly expressed in 55% of PTCs compared to other thyroid cancers [21]. However, TGFβRII protein and mRNA expression display reduced levels in thyroid cancer cells [17] [21].

TGF-β is abundant in the tumour microenvironment. It stimulates all cell populations including tumour cells, fibroblasts, and endothelial cells. Moreover, it enhances motility and recruitment of immune cells including monocytes, macrophages, NK cells, dendritic cells and T-cells while directly inhibiting their anti-tumour functions [22] [23].

We decided to analyse the immunohistochemical expression of TGF-β1 and its downstream phosphorylated SMAD4, element and of the inhibitory SMAD7 in PTC variants and their association with the localisation of TAMs within the tumour microenvironment.

Material and Methods

Tumor samples

A series of 69 PTC cases has been retrieved from the Archives of the University Hospital in Stara Zagora, Bulgaria. The group of patients with PTC include cases with lymph node metastases (n = 2 or 2.9%) and without metastases and without metastases (n = 67 or 97.1%). The mean follow-up of 152.58 months; range from 1.64 to 197.07 has been done. PTC tumours were classified by size into tumours 1cm or less in greatest dimension and tumours more than 1cm in greatest dimension. There are 9 (13.0%) men and 60 (87.0%) women with age ranging from 22 to 81 years (mean 51.84 ± 13.756). Among the 69 PTC studied, 6 are ≤ 1 cm in diameter, and 63 tumours are larger. According to AJCC classification [24], 42 of the patients (60.8%) are in stage I, 20 of the patients (29.0 %) are in stage II, 7 of the patients (10.2%) are in stage III, and no patients are in stage IV of the disease, (Table 1).

Table 1: Demographic, clinical data, histological and pathological characteristics of the tumour specimens according to the papillary thyroid tumour type

Characteristics	PTC N (%)
Age (mean ± SD)	54.17 ± 14.48
Gender	
Males	9 (13.0)
Females	60 (87.0)
Pt classification	
T1-T2	64 (92.7)
T3-T4	5 (7.3)
Lymph node metastases	
N0	67 (97.1)
N1	2 (2.9)
Distant metastases	
M0	69 (100)
M1	0 (0)
Ptnm staging	
I stage	42 (60.8)
II stage	20 (29.0)
III stage	7 (10.2)
IV stage	0 (0)
Differentiation	
Well	69 (100)
Poorly	0 (0)
Capsule	
Non	9 (13.0)
Presence	60 (87.0)

* - ANOVA test; ** - $\chi 2$ test.

The study protocol has been approved by the Research Ethics Committee of University Hospital Stara Zagora.

All samples have been fixed in formalin and embedded in paraffin. Clinical data has been collected from the pathology reports, clinical files and Oncology Dispensary. H&E slides are retrieved from the archives, and they have been reviewed independently by two pathologists (MG and KI), and the tumours are classified using the WHO criteria [25]. Cases with doubtful PTC features are excluded.

Immunohistochemistry

Immunohistochemical staining is performed using the streptavidin-biotin technique as previously described [26]. Briefly, the endogenous peroxidase is blocked with 3% hydrogen peroxide in methanol for 10 min. Slides are incubated over night at room temperature with primary antibodies as follows: TGF - β (Clone sc-146) antibody in a dilution 1:50; monoclonal mouse anti-SMAD4 antibody (Clone sc - 7966) in a dilution 1:100; monoclonal mouse anti-SMAD7 antibody (Clone sc-11392) in a dilution 1:100; monoclonal mouse anti-TGFβ RII antibody (Clone sc-400) in a dilution 1:100-all produced from Santa Cruz Biotechnology, CA and monoclonal mouse anti-CD68

antibody (Clone KP11 M0814) ready–to-use, has been purchased from DAKO, Glostrub, Denmark. Then the slides are incubated with biotinylated secondary antibody and streptavidin-peroxidase complex for 2 hours and room temperature. Tissue sections with adequate positive and negative controls are used in every set of straining. Finally, sections are weakly counterstained with Mayer's hematoxylin.

Semi-quantitative assessment of TGF-β1, SMAD4, SMAD7, and TGFβRII

The TGF-β1 expression is evaluated in the cytoplasm of tumour cells, TGFβRII expression is evaluated in tumour cell cytoplasm and membrane. SMAD4 and SMAD7 are evaluated in tumour cell cytoplasm and tumour cell nucleus. The immunohistochemical expression is evaluated as absent (0) and present (+) in tumour cell cytoplasm and nuclei. The TGF-β1 expression is also evaluated in the centre and periphery of all thyroid cancers (PTC) and in the respective remaining thyroid tissue, which has been used as an internal control. TGF-β1 expression, detected in thyrocytes in the control tissue is considered as the basal expression.

The expression of SMAD4 and SMAD7 is evaluated in all PTCs and in the respective remaining thyroid tissue, which has been used as an internal control tissue and considered as a basal expression. The expression of SMAD4 and SMAD7 has been not evaluated in the centre and periphery since it is considered too difficult to distinguish and therefore assumed as similar. Their expression is also graduated in two categories: absent and present (weak, moderate and intense staining) regarding each subcellular location (nuclear and cytoplasmic) separately.

Macrophage counting

A single pathologist (MG), who is blinded to the clinical assessments of each case, has scored the cases by counting, the number of CD68 TAMs in five independent fields of vision in a tumour and the invasive front under a 400 x magnification. $CD68^+$ cell counts are expressed as the mean ± standard deviation.

Patients' slides with PTC assessed parameters

Clinicopathological parameters. On H&E slides the following parameters are evaluated: capsule formation, capsule infiltration, vascular invasion and from protocols – extra-thyroid extension, metastases, multicentricity and tumour size of micro-carcinomas are checked. Patients are followed up until January 2016.

Statistical analysis

The SPSS 16.0 program for Windows was used for statistical analysis. The chi-squared test and Fisher's exact test were used to compare the immunohistochemical staining and the clinicopathological parameters. ANOVA, Student – t-test, Mann-Whitney U test and Kruskal-Wallis test were applied for comparing the continuous variables depending on the normality of the distribution. Correlations were tested by Spearmen and Person tests. Survival plots were drawn by the Kaplan–Meier test and survival periods were compared by log-rank test. The accepted level of significance was set at $p < 0.05$.

Results

Components of TGF-β1 pathway in tumour tissue

The TGF-β1 expression is detected mainly in tumour cell cytoplasm and is weakly demonstrated in tumour cell membranes. As compared to TGF-β1 expression, TGFβRII immune reaction is weaker in tumour cell cytoplasm (17.8%).

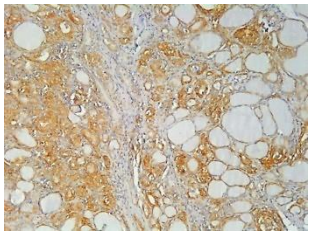

Figure 1: Positive expression of TGF-β1 in tumour border (x 100)

The TGF-β1 expression is not significantly correlated to any other clinical or pathological parameters. The cytoplasmic expression of TGF-β1 is directly proportional to the expression of both SMAD4 and SMAD7.

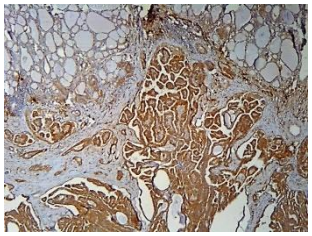

Figure 2: Positive expression of TGF-β1 in tumour cytoplasm and tumour border in micro-papillary thyroid cancer (x 100)

Lack of expression of TGF-β1 and SMAD7 in tumour cell cytoplasm is associated with capsule formations around tumour tissue. The SMAD4 nuclear expression is observed in 8.1% (n=4 patients) of tumours. There is not a significant difference between

TGF-β1 expression at the periphery of each a tumour and in its centre.

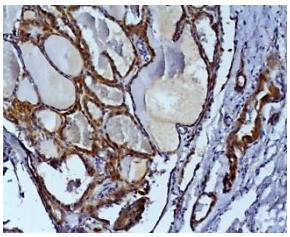

Figure 3: TGFβRII positive, strong expression (x 200)

The expression of SMAD4 and SMAD7 in tumour nuclei is insignificant. The SMAD4 strong cytoplasmic expression is observed in 11 patients (24.4%) and weak positivity in 26 patients (57.8%).

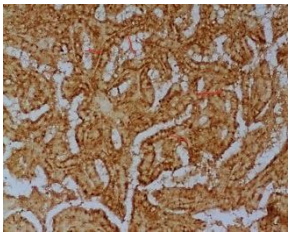

Figure 4: Positive expression of Smad4 in tumour nuclei (x 100)

The SMAD7 strong cytoplasmic expression is observed in 3 patients (6.7%) and weak positivity in 27 patients (60%). TGF-β1, TGFβRII, SMAD4 and SMAD7 cytoplasmic expression is not significantly associated with any clinical or pathological parameters, (Figure 1-5).

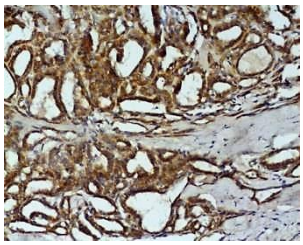

Figure 5: Strong positive expression of Smad7 in tumour cytoplasm (x 200)

Characterization of TAMs in PTC

The CD68 immunohistochemistry effectively stains macrophage cytoplasm. The TAM nuclei in PTC tissue are approximately 1/3 to ½ of the size of the nuclei of tumour cells. TAMs had cellular projections that wrap around tumour cells. TAMs and cancer cells appeared to be in close contact (Figure 6). TAMs formed distinctive canopy-like structures over some tumour cells.

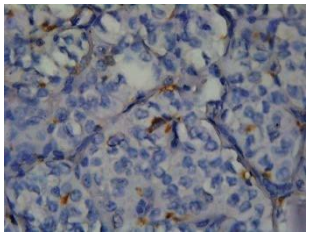

Figure 6: CD68-positive macrophages with canopy-like structures (x200)

Correlations between clinic-pathologic parameters, TGF-β1, TGFβRII, SMAD4 and SMAD7and CD68-positive TAM densities

As histologic grade (type) of thyroid cancer is an important determinant of tumour behaviour and clinical prognosis, it is important to explore the effect of TAMs and TGF-β1 signalling pathway proteins on some clinic-pathologic parameters. There is no statistical correlation between the presence of TAMs (high or low density) and extra-thyroidal extension, capsular invasion and vascular invasion. The intense TGF-β1, SMAD4 and SMAD7 expression in tumour cell cytoplasm correlated with increased CD68+ TAMs number in tumour stroma (and for TGF-β1 in the invasive margin). There were no differences between patients with or without increased CD68- positive TAMs in gender, age, tumour stage and grade (Table 3).

Table 2: Associations between the presence of CD68-positive cells in tumour border and the invasion front of tumours with the expression of molecules involved TGF-β1 signalling pathway

Expression level of TGF-β1 signalling pathway molecules	№	CD68 in tumour border N (%)		CD68 in tumour stroma N (%)	
		Low numbers (less than 5.57-50th percentile)	High numbers (less than 5.57-50th percentile)	Low numbers (less than 11.80-50th percentile)	High numbers (less than 11.80-50th percentile)
TGF-β1 in tumour stroma					
Negative n (%)	17	3 (17,64)	14 (82,35)	9 (52,94)	8 (47,05)
Positive n (%)	34	21 (52,5)	19 (47,5)	20 (58,82)	14 (41,17)
P value		0.015*		0.689	
TGF-β1 in tumour border					
Negative n (%)	22	8 (36,36)	14 (63,63)	5 (50,00)	5 (50,00)
Positive n (%)	29	16 (55,17)	13 (44,83)	24 (58,53)	17 (41,47)
P value		0.183		0.625	
SMAD4 in tumour stroma					
Negative n (%)	17	7 (41,17)	10 (58,82)	10 (58,82)	7 (41,17)
Positive n (%)	34	17 (70,83)	7 (29,16)	19 (55,88)	15 (44,12)
P value		*0.058***		0.842	
SMAD4 in tumour border					
Negative n (%)	27	15 (40,45)	22 (59,45)	10 (55,55)	8 (44,44)
Positive n (%)	14	9 (64,28)	5 (35,71)	19 (57,57)	14 (42,42)
P value		*0.129****		0.889	
SMAD7 in tumour stroma					
Negative n (%	30	13 (43,33)	17 (56.66)	18 (60,00)	12 (40,00)
Positive n (%)	21	11 (52,38)	10 (47,61)	11 (52,38)	10 (47,61)
P value		0.524		0.589	
SMAD7 in tumour border					
Negative n (%)	25	17 (68,0)	8 (32,0)	15 (60,0)	10 (40,0)
Positive n (%)	26	12 (46,15)	14 (53,84)	9 (34,61)	17 (65,38)
P value		*0.069***		*0.115****	

X^2 - test: * The values in bold shown statistical significance; ** Values in bold italic shown (border) importance; *** The values in italic shown tendency.

From the analysis of CD68- positive cells in tumour border and tumour stroma correlated with expression of TGF-β1/SMAD proteins, we observed that the positive expression of TGF-β1 in tumour cytoplasm, significantly correlated with increased number of CD68-positive cells in tumour border (χ^2 = 5.945; p = 0.015). Our work also revealed marginal significantly of Smad4 in tumor cytoplasm as compared to increased number of macrophages in tumor border (χ^2= 3.606; p = 0.058), and a tendency for Smad7 in tumor border correlated with increased number of CD68-positive cells in tumor stroma (p = 0.115), (Table 2 and 3).

Table 3: Association between various clinic-pathological factors with the number of CD68-positive cells in tumour stroma and tumour border

Characteristics	№	CD68+ cell in tumour stroma mean ± SD	P value	CD68+cell in tumour border mean ± SD	P value*
Age (mean ± SD)					
<53,28	30	22.85 ± 20.27		51.99 ± 9.49	
>53.28	39	16.46 ± 21.30	0.227	34.51 ± 6.76	0.484
Gender					
Males	9	20.77 ± 23.08		15.26 ±18.48	
Females	60	19.71 ± 20.62	0.898	28.17 ± 48.17	0.467
Pt classification					
T1-T2	64	20.82 ± 21.53		31.97 ± 46.31	
T3-T4	5	35.23 ± 24.76	0.177	36.44 ± 71.83	0.565
Lymph node metastases					
No	2	30.55 ± 35.14		30.55 ± 35.14	
Yes	67	22.07 ± 21.87	0.385	22.07 ± 21.87	0.647
Ptnm staging					
I=II	62	20.29 ± 21.20		32.03 ± 47.56	
III-IV	7	33.89 ± 24.90	0.143	34.80 ± 58.76	1.000
Differentiation					
Well	69	26.16 ± 24.84		41.44 ± 54.90	
Poorly			1.000		0.452
Capsule					
None	9	19.50 ± 22.32		29.98 ± 54.91	
Present	60	24.33 ± 22.38	0.177	34.58 ± 49.11	0.937

* Mann-Whitney U test.

Patients with low infiltration with CD68-positive cells in tumour stroma have significantly shorter overall survival (median of 129.267 months) compared to those with high CD68-positive cells infiltration (median is not reached, p = 0.034, Log-rank test).

Discussion

Our study demonstrates that TGF-β1, SMAD4, SMAD7 and TGFβRII protein expression is observed in PTC tumour cells and these proteins are overexpressed in tumour cells as compared to the surrounding normal thyroid tissue. We couldn't find any difference in the expression of TGF-β1 signalling proteins in tumour centre and periphery as did Eloy et al. (2012). Moreover, the number of patients with PTC is similar in both studies (75 patients in Eloy at al., 2012; 80 patients in our study). Our PTCs are mainly well-circumscribed, and we don't subdivide them to well-circumscribed papillary thyroid cancer (WCPTC) and poorly-circumscribed papillary thyroid cancer (PCPTC), respectively as Eloy et al., 2012 do. These authors establish that in WCPTCs the differences of TGF-β1 expression from centre to the periphery are very insignificant. We detect that TGF-β1, SMAD4 and SMAD7expression in all cases of PTC and control tissues (except in 17 TGF-β1 negative cases) are similar to that reported previously [2] [11] [18]. SMAD4 cytoplasmic/nuclear expression is considered to be indicative of a functioning TGF-β (SMAD-dependent pathway) [11] [19]. In our study, it is demonstrated that all tumours expressed SMAD4 in their cytoplasm to a lesser extent than TGF-β1. It is known that the lower expression of SMAD4 was mainly responsible for the impairment TGF-β signalling [19]. In a previous study, the authors demonstrated that *SMAD4* mutations are frequent in PTC [27] when sequencing of the entire coding part of the *SMAD4* gene was performed. In later study D'Inzeo et al., 2010 hypothesised that the cause of lower expression of SMAD4 could be found in alteration of major components of translational machinery, which are frequently altered in human neoplasms [28]. The molecular mechanism that controls subcellular localisation and activation of Smad proteins is crucial for TGF-β signalling, and it is not yet fully clarified. It has been shown that SMAD4 nuclear expression is reduced in cancer [19]. However, SMAD4 undergoes continuous nucleocytoplasmic shuttling on its own, independently of TGF-β signalling [29]. The levels and the duration of residence in the nucleus of SMAD4 are important events for the response of TGF-β in the cells, and the intensity and duration of the TGF–β-Smad response is important for the signalling specificity. There we demonstrate the reduction of SMAD4 protein expression in PTC tumour cell cytoplasm and in nuclei which may be indicative of a loss of TGF-β cytostatic response (loss of tumour cell growth inhibition). Therefore the reduction of SMAD4 cytoplasmic and loss of nuclear protein expression is associated with the embarrassment of the TGF-β signalling pathway.SMAD7 nuclear expression was associated to loss of TGF–β/Smad–dependent pathway inhibition [2], and its expression is found to be at basal levels and lesser as compared to TGF-β1 and SMAD4 expression of the cases in the presents series-similarly to other reports [11]. TGF-βRII mRNA overexpression was detected in PTC cell lines [17]. In our study, TGF-βRII expression was lower as compared to TGF-β1 expression in tumour cells of PTC.

We demonstrate that all investigated from TGF–β/Smad pathway proteins in our study are associated with increased CD68 TAMs density in tumour stroma and the border of PTCs. It has been shown that large cohorts of cancers including thyroid cancer with high-density TAMs have poor prognoses and poor survival rates [30].

The impact of TGF-β signalling in the immune system was well documented. TGF-β promotes recruitment of monocytes, and it has been hypothesised that TGF-β can promote monocytes to

macrophage differentiation [1]. Moreover, TGF-β stimulation of macrophages had been shown to attenuate macrophages associated suppression of $CD4^+$ T cell proliferation. TGF-β signalling is needed for the alternative activation of macrophages to M2 status. It has been shown that lack of TGF-βRII leads to the defects in the expression of a set of genes that form the hallmark of the M2 polarising program [22].

Therefore, TGF-β enhances motility and stimulates recruitment of monocytes, macrophages and other immune cells while directly inhibiting their anti-tumour effector functions [31]. As a result, TGF-β associated inflammation can promote tumorigenesis due to secretion of growth-factors, cytokines, chemokines, etc. from the recruited immune cells that stimulated cancer cell growth, motility and invasion.

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Basic Science

Proton Pump Inhibitors Intake and Iron and Vitamin B12 Status: A Prospective Comparative Study with a Follow up of 12 Months

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Abstract

BACKGROUND: Proton pump inhibitors (PPIs) represent the most widely prescribed antisecretory agents, but their prolonged use, may influence iron and vitamin B12 status, which could have important implications for clinical practice.

AIM: We undertook this study aiming to investigate the association between PPIs use for 12 months and potential changes in iron and vitamin B12 status, as well as whether this potential association varies among four specific PPI drugs used in the study.

METHODS: A total of 250 adult subjects were recruited into this study, of which 200 subjects were PPIs users while 50 subjects belonged to the control group. Serum iron, ferritin, vitamin B12, and homocysteine (Hcy) levels were measured before the start of the study and after 12 months. Mann - Whitney U test and Kruskal - Wallis test was used to compare the baseline characteristics of the study groups, while Wilcoxon test was used to analyse post - pre differences.

RESULTS: Statistical analysis showed significant changes within PPIs group and specific PPIs subgroups between the two-time points in serum ferritin and vitamin B12 levels, respectively, while no significant changes in serum iron and homocysteine levels were shown. However, subsequent diagnosis of hypoferremia and hypovitaminosis B12 in the whole study sample at 12 months was established in only 3.8% and 2.9% of the subjects, respectively.

CONCLUSION: PPIs use for 12 months did not result in clinically significant iron and/or vitamin B12 deficiency; thus, these findings argue routine screening under normal circumstances, although monitoring in elderly and malnourished may be of precious value.

Introduction

Proton pump inhibitors (PPIs) represent the most widely prescribed antisecretory agents [1] Prolonged PPIs use is not without consequences, however [1] [2]. Concerns have been raised about a possible association between prolonged PPIs use and increased risk for vitamin and mineral deficiencies [3] [4]. It has been suggested that their prolonged use may influence iron and vitamin B12 status due to potent suppression of gastric acid secretion by parietal cells, which could have important implications for clinical practice [5] [6]. Relatively few studies have specifically investigated the association between PPIs use and iron status and/or risk of anemia while what is known about the association between PPIs use and vitamin B12 deficiency is largely based on case - reports or retrospective observational studies with considerable inconsistency in the findings [7] [8] [9] [10] [11] [12] [13] [14] [15] [16]. Moreover, they have failed to provide appropriate monitoring

recommendations in this regard [17]. Most of the previous studies provided only the data comparing "treatment" with "no treatment", we therefore undertook this study aiming to prospectively investigate the association between PPIs use for 12 months in new - users and potential changes in iron and vitamin B12 status, as well as whether this potential association varies among four specific PPI drugs used in the study. Also, the incidence of new-onset hypoferremia and hypovitaminosis B12 and hyperhomocysteinemia (HHcy) during the study was assessed.

Material and Methods

The methodology of this open - labelled prospective study is described in greater detail elsewhere [18] [19]. Briefly, the study population consisted of subjects aged 18 to 65 years with a confirmed diagnosis of osteoarthritis of small joints of the hands and on chronic NSAIDs that indicated to initiate gastroprotective maintenance therapy with PPIs. Control group consisted of 50 matched healthy participants and with no gastrointestinal or other risk factors present for iron and vitamin B12 deficiency. The participants belonging to the groups under treatment with PPIs were contacted every 3 months by telephone to assess the adherence to PPIs and the potential adverse effects, while participants in the control group were contacted by telephone after 12 months.

Subjects were enrolled in the study only if they had serum iron, ferritin and vitamin B12 levels greater than lower reference limit provided by the lab (Table 1). Subjects were not included in the study if they were using parenteral and/or oral supplements of iron, vitamin B12 and folic acid, respectively, as well as any of the antisecretory agents (including PPIs) during preceding 12 months. Also, subjects with known hypersensitivity to any drug were excluded. Subjects were also excluded from the study if they were blood donors, were on vegetarian diet, were chronic alcohol abusers, were using concomitantly drugs (namely metformin, thyroid hormone supplements, antiepileptic drugs, anticoagulant drugs, oral contraceptives, glucocorticoids) and/or had diseases that may affect iron and vitamin B12 status (namely dementia, acute inflammatory diseases, malabsorption diseases, abnormal uterine, gastrointestinal or urinary bleeding, patients with atrophic gastritis or gastrectomy, thyroid diseases, renal diseases, cardiovascular diseases, neoplastic diseases including leukemias and lymphomas). Subjects were not included if they were pregnant, lactating or planning a pregnancy. To enhance the validity of our findings all the potential study participants were screened for exclusion mentioned above criteria.

A total of 250 adult subjects were recruited into this study, of which 200 subjects were PPIs users of orally taken dosage forms of PPIs while 50 subjects belonged to the control group (PPIs nonusers). PPIs users were divided into four matched groups, each of them consisting of 50 subjects: patients on omeprazole therapy (20 mg/day), patients on esomeprazole therapy (20 mg/day), patients on lansoprazole therapy (30 mg/day), and patients on pantoprazole therapy (40 mg/day).

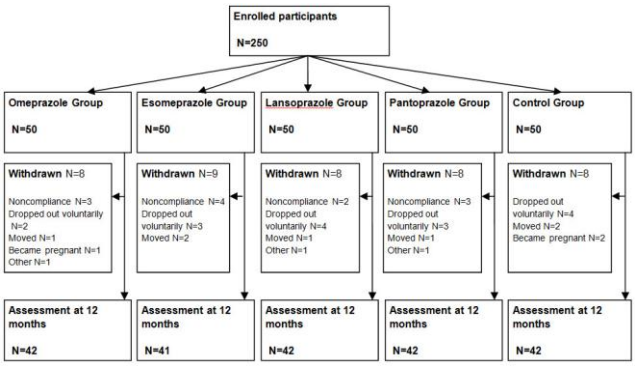

Figure 1: Study design [18]

All study participants provided written informed consent. Before the initiation of the study was obtained the approval of the study protocol from the local ethical committees of the University Clinical Center of Kosova and Faculty of Medicine, University of Prishtina.

Fasting blood samples were collected from the antecubital vein at 8 AM, and were centrifuged within the first hour to separate the serum. The measurements of serum iron, ferritin, vitamin B12 and homocysteine levels were done before the start of the study (at baseline) and after 12 months. Serum iron, ferritin and homocysteine (enzymatic test) concentrations were measured simultaneously using automated analyser, COBAS Integra 400 Plus (Roche Diagnostics, Switzerland), while serum vitamin B12 concentrations were measured by Electrochemiluminescence Immunoassay using Elecsys 2010 system (Roche Diagnostics, Switzerland). Hypoferremia was defined as serum levels of <10.6 μmol/l in male and < 6.6 μmol/l in female, hypoferritinemia was defined as serum levels of < 30 ng/ml in male and < 13 ng/ml in female, hypovitaminosis B12 was defined as serum levels of < 191 pg/ml, and hyperhomocysteinemia was defined as serum levels of >15 μmol/l.

All the study results are expressed as the mean ± standard deviation and as percentages, as appropriate. The baseline continuous characteristics of the study groups were compared by using Mann - Whitney U test and Kruskal-Wallis test, as appropriate, while baseline categorical characteristics

were compared by using the chi-square test. The Wilcoxon signed-rank test was used to analyse post - pre differences in biochemical parameters. All statistical analyses were done with SPSS, version 20. A value of $p < 0.05$ was considered statistically significant.

Results

Out of a total of 250 participants that were initially recruited in the study, 209 participants completed 12 months of study. Thus only their data were analysed and presented here. The most common reasons for withdrawal from the study were non - compliance, changes in the place of residence and loss of follow - up, pregnancy and other personal reasons (Fig. 1). Most participants were female (74.6%), and the mean age at the beginning of the study was 50.59 ± 10.61 years. Mann - Whitney U test and Kruskal - Wallis test showed no significant differences in the baseline study characteristics between groups and subgroups (data not shown).

Table 1: One-year changes in biochemical parameters according to study groups

Biochemical parameters	PPI users (*n*=209)		*p*-value	PPI non-users (*n*=42)		*p*-value
	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment	
Homocysteine (5.5-15 µmol/l)	14.22±3.3	14.5±4.3	0.32	14.7±4.3	13.8±3.2	0.08
Vitamin B_{12} (191-663 pg/ml)	433.6±122.5	393.5±139.4	<0.001	418.9±127.3	416.2±115.6	0.66
Ferritin (ng/ml)[a]	135.2±111.2	94.1±76.2	<0.001	105.8±87.4	87.6±82.8	0.21
Iron (µmol/l)[b]	17.6±5.23	16.9±5.4	0.049	19.0±4.9	19.6±4.9	0.14

p-values according to Wilcoxon signed-rank test; [a] ♂: 30 - 400 ng/ml, ♀: 13 - 150 ng/ml; [b] ♂: 10.6 - 28.3 µmol/l, ♀: 6.6 - 26.0 µmol/l.

The results of the Wilcoxon signed - rank test summarised in Table 1 showed the statistically significant difference between the baseline and 12 months' serum ferritin and vitamin B12 levels within PPI group ($p < 0.001$ for both parameters). When specific PPI subgroups were analyzed (Table 2), the Wilcoxon signed - rank test showed that the most significant difference in mean serum ferritin levels was in pantoprazole group ($p < 0.001$), while the least, but still significant difference, was in omeprazole group ($p = 0.01$); as for serum vitamin B12 levels, the most significant difference was in lansoprazole group ($p = 0.004$).

Although the statistical analysis did not show any statistically significant difference in the mean iron serum levels between specific PPI subgroups (Table 2), when all the study subjects under active treatment with PPIs were considered as a single group (Table 1), the difference reached a borderline statistical significance ($p = 0.049$).

No statistically significant difference in the mean homocysteine serum levels was noticed within PPI group and specific PPI subgroups; nevertheless, after 12 months, the incidence of the new - onset hyperhomocysteinemia in the whole study sample was 35.4 %, with sixty - six cases (39.5%) among PPIs users and eight cases (19.0%) among PPIs non-users (39.5% vs 19.0%, $p = 0.013$).

No statistically significant differences between PPIs users and non-users were noticed in the incidences of the new-onset of hypoferritinemia, hypoferremia and hypovitaminosis B12 (7.2% vs. 9.5%, $p = 0.610$, 4.8% vs. 0%, $p = 0.148$ and 3.0% vs. 2.4%, $p = 0.832$, respectively).

Table 2: One - year changes in biochemical parameters according to study subgroups

	Biochemical parameter	Pre-treatment	Post-treatment	*p*–value
Omeprazole group (n=42)	Homocysteine	14.3±3.9	14.5±3.0	0.48
	Vitamin B_{12}	404.9±111.7	381.6±122.9	0.02
	Ferritin	133.1±101.1	99.5±87.9	0.01
	Iron	17.6±5.7	16.2±6.1	0.13
Esomeprazole group (n=41)	Homocysteine	14.1±3.0	14.5±2.3	0.19
	Vitamin B_{12}	439.4±128.4	395.6±156.6	0.02
	Ferritin	121.0±105.5	91.2±67.8	0.001
	Iron	17.8±4.4	17.4±4.3	0.29
Lansoprazole group (n=42)	Homocysteine	14.9±3.4	15.1±2.7	0.79
	Vitamin B_{12}	438.2±127.3	396.6±143.7	0.004
	Ferritin	138.7±114.7	93.3±76.7	0.001
	Iron	18.2±6.3	17.6±5.9	0.64
Pantoprazole group (n=42)	Homocysteine	13.5±2.6	13.9±7.2	0.81
	Vitamin B_{12}	452.1±121.4	399.9±137.2	0.01
	Ferritin	147.6±124.3	92.4±73.4	<0.001
	Iron	16.9±4.6	16.8±5.2	0.30
Control group (n=42)	Homocysteine	14.7±4.3	13.8±3.2	0.08
	Vitamin B_{12}	418.9±127.3	416.2±115.6	0.66
	Ferritin	105.8±87.4	87.6±82.8	0.21
	Iron	19.0±4.9	19.6±4.9	0.15

p-values according to Wilcoxon signed-rank test; All the parameters are expressed as mean± standard deviation;

It is noteworthy that no statistically significant difference was shown in the control group in any of the biochemical parameters of the study.

Discussion

The results of the current study indicate a significant association between PPIs use for 12 months and reduction in iron body stores and vitamin B12 levels and higher prevalence of HHcy among PPI users. Our findings suggest that prolonged PPIs therapy affects iron and vitamin B12 status. Nevertheless, the subsequent diagnosis of hypoferremia and vitamin B12 deficiency at the end of the study was established in only 3.8% and 2.9% of the subjects, respectively, without significant differences between PPIs users and non - users.

Early studies that noticed the association between clinical conditions associated with achlorhydria or hypochlorhydria and diminished intestinal iron absorption raised interest about the potential effect of prolonged PPIs therapy on iron status [7] [20]. Years later, through mutations on proton pumps on rats, Krieg et al. [21] confirmed the necessity of gastric proton pump for iron absorption. Nevertheless, the number of studies that have

specifically investigated the association between prolonged PPIs use and iron status is relatively small. Among the first studies to suggest such an association is a case report of two anemic patients [12], in whom no response to oral substitutive therapy with iron was noted when the patients continued to take PPIs, while their iron status improved after PPIs withdrawal; this made the authors to attribute the nonresponsiveness to iron therapy to PPIs. In another study on patients with hereditary hemochromatosis that require frequent phlebotomies [22], administration of PPIs (omeprazole or lansoprazole) for 7 days resulted in significant reduction in the amount of blood removed per annum to maintain adequate iron body stores (ferritin levels of ~50 μg/l). A retrospective cohort study of Sarzynski et al. [13] on adult outpatients who have been on PPI therapy for at least one year, demonstrated a significant reduction in hematologic indices compared to baseline values. Similarly, in a recent retrospective study of Shikata et al. [23] proved that PPIs use was associated with anaemia in cardiovascular outpatients, thus reporting a high frequency of anaemia among PPIs users compared to non-users (51% vs 19%, $p < 0.001$).

The findings from this study indicate significant changes in iron body stores (serum ferritin levels) among PPIs and specific PPIs subgroups between the two time points, while no significant changes in serum iron levels (except for borderline significance when PPIs users as a single entity), and speak for pre-latent iron deficiency that is actually the initial phase in the pathogenesis of iron deficiency anemia.

In recent years there has been growing interest in the relationship of PPIs prolonged use and vitamin B12 deficiency; however, there is still considerable uncertainty about providing monitoring recommendations [10] [24] [25]. The potential mechanisms behind the increased risk of vitamin B12 deficiency in prolonged PPIs users are vitamin B12 malabsorption and bacterial overgrowth in the gut [3] [4].

Marcuard et al. [8] were among the first to prove dose-dependent reduction of absorption of cyanocobalamin in healthy volunteers on short-term therapy with omeprazole for two weeks; nevertheless, an increased risk for vitamin B12 deficiency due to long-term use of PPIs was first reported by Termanini et al. [9] in a prospective study performed on patients with Zollinger-Ellison syndrome. In the last few years, much more information has become available about the association between long-term use of PPIs and vitamin B12 deficiency [10] [11] [24] [26]. More recent studies of Lam et al. [14] and Lewis et al. [25] have also indicated the presence of vitamin B12 deficiency in patients exposed to chronic PPIs.

The findings from this study lend support to previous findings in the literature with data analysis indicating significant changes in vitamin B12 levels among PPIs users and specific PPIs subgroups at 12 months as well as significantly higher in-study incidence of HHcy among PPIs users. Nevertheless, Hcy serum levels in PPIs users resulted in a slight but non-significant increase, that might seem controversial at first because Hcy reflects the functional status of vitamin B12, but it can be explained by the fact that higher levels of Hcy are more prevalent in lower levels of vitamin B12, and vitamin B12 deficiency was established in only 2.9 % of the subjects.

On the other hand, we should mention that there are studies that do not support our findings of the association between long-term use of PPIs and vitamin B12 deficiency [7] [27] [28]. The main reason(s) for this inconsistency in findings is still not completely clear.

We are aware that our study might have certain limitations. The first might be sample size as it was arbitrarily chosen. Another one is the inability to assess dietary intake of iron and vitamin B12. Unfortunately, we were unable to measure folic acid serum levels and methylmalonic acid serum levels, a specific marker of vitamin B12 status, which might have also influenced the results.

In conclusion, in spite of the fact that significant changes on ferritin and vitamin B12 serum levels among PPIs users were shown, PPIs use for 12 months did not result in clinically significant iron and/or vitamin B12 deficiency. These findings argue routine screening under normal circumstances; however, considerable attention must be paid when PPIs are prescribed in elderly and malnourished, where monitoring may be of precious value.

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Basic Science

Is the rs1801282 (G/C) Polymorphism of *PPAR - Gamma* Gene Associated with T2DM in Iraqi People?

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Abstract

BACKGROUND: Pro12Ala (rs1801282) is a common polymorphism of the human *PPAR-γ* gene. Studies have demonstrated conflicting results about its association with T2DM worldwide. There are no reports about such possible association among Iraqi people.

OBJECTIVES: This study aims at finding out whether having the mutant allele (Ala12) might be associated with T2DM among Iraqi people.

METHODS: One hundred and ninety-two Arabic Iraqi adult subjects (97 with T2DM and 95 controls) were genotyped using PCR- RFLP. Clinical, anthropometrical and biochemical variables were compared regarding the Pro12Ala genotypes.

RESULTS: About 5.67% of people with diabetes were carriers of the (Ala12) allele versus 9.47% of controls. Allelic and genotypic frequencies were not statistically different among diabetics and controls [(χ2= 1.99, p= 0.16) and (χ2= 2.17, p= 0.14)]. Age, BMI and smoking- but not Pro12Ala - were independent risk factors for T2DM in our subjects. Pro12Ala was not associated with T2DM (Odd's ratio 0.55, 95% CI 0.23- 1.32, p= 0.14).

CONCLUSIONS: Our study revealed a relatively high frequency of the Ala12 allele among Arabic Iraqis. These frequencies did not significantly differ between diabetics and controls indicating the absence of association of Pro12Ala with T2DM among Iraqis.

Introduction

Diabetes Mellitus (DM) is a heterogeneous group of metabolic disorders that occur as an ultimate result of defective endogenous insulin secretion and/or action [1]. The genetic contribution in the pathogenesis of type 2 diabetes mellitus (T2DM) is remarkable given the inheritance is seen in families, the high prevalence rates of the disease in certain ethnic groups compared to others and the difference in the concordance rates when monozygotic twins are compared to dizygotic ones [2] [3]. The genetic background of T2DM has shown to be a cocktail as described by Freeman and Cox who suggested that understanding the basis of the genetic traits of T2DM can help identify new therapeutic targets, which currently represents one of the most promising strategies for the long-term treatment success [4].

Scientists have used their tools for exploring the genetic background of T2DM including “Genome Scans” and “Association studies”. The association studies, including Genome Wide Association Studies (GWAS), are case-control studies that investigate the relationship of particular disease status with certain alleles, genotype (or haplotype) or most commonly a set of single-nucleotide polymorphisms (SNPs) [4] [5] [6] [7]. The GWAS(s) which were first successfully conducted in 2005 is a major tool for identifying different biological pathways, understanding the pathophysiology of several complex (multifactorial) diseases and developing drug therapies [7]. They typically conduct the first analysis in an exploration cohort and then validate the most significant genetic findings (mainly SNPs) in an independent validation cohort [8].Several association studies have identified some key genes for human T2DM susceptibility of which the peroxisome proliferator-activated receptor gamma (*PPAR-γ*) and the *KCNJ11* are the most promising genes [9] [10]. However, using the candidate gene approach, other several genes have been recently confirmed as susceptibility genes like *CAPN10, HNF4A, TCF7L2, BCL11A, MTNR1B,*

NOTCH2/ADAM S30, DCD, VEGFA, GCK, FTO, HHEX/IDE, JAZFI, KCNQ1, CYP3A4, and others [11].

Peroxisome proliferator-activated receptors are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily [12]. Their activation through their ligands binding leads to augment the expression of many genes especially those involved in lipid metabolism and energy homeostasis [13] [14]. There are three well-identified types of *PPARs; PPAR α, PPARδ* (or *PPARβ*) and *PPARγ*. The DNA- binding domains of the three subtypes are about 80% identical [15].

Human *PPAR γ* gene is located on chromosome 3 (3p25), and it spans a genomic segment of around 150 kb. It consists of 9 exons (A1, A2, B and 1-6) that code for the two major isoforms of PPAR γ mRNA and protein (PPAR γ1 and PPAR γ2) via the use of different promoters and alternative splicing [16].

In humans, PPAR γ2 is mainly expressed in the adipose tissue, and it is a critical transcriptional factor in the regulation of adipocytes differentiation and the expression of many genes that are responsible for lipogenesis and insulin signalling [17]. PPAR γ agonists –whether natural like polyunsaturated fatty acids or synthetic like the antidiabetic drugs thiazolidinediones- have been shown to improve the overall body insulin sensitivity in a variety of insulin resistant experimental animals and diabetic humans [18] [19].

A common C→ G polymorphism of *PPAR-γ* gene results in a proline to alanine substitution at the codon 12 of the gene (Pro12Ala) with a reduced transcriptional activity of the resultant protein [20] [21]. The minor allele (Ala12 allele) frequency of this common gene variant is widely variable worldwide. It was found to range from 5.9% to 21.6% among Caucasian ethnicities, and from 1.7% to 9.3% among people of East Asian descent such as Chinese and Japanese [22].

There has been conflicting results about the association of Pro12Ala mutation of *PPAR- γ* gene with T2DM in different populations [23] [28]. We hypothesize that this variant is linked to the risk of T2DM in Iraqi people as well due to its possible impacts on insulin action and/or signaling pathways and that the inconsistent findings concerning its association with diabetes around the world is a reflection of the multifaceted interactions between this polymorphism and various environmental factors (including the different fatty acids contents in people diet world-wide) and/or between this sequence variation and other genetic factors.

In fact, there have been no studies on the association of Pro12Ala (rs1801282) of *PPAR-γ* gene with T2DM in Iraqi people. So, this study aims to find out whether having its mutant allele (Ala12) is associated to T2DM in a representative sample of adult Iraqi people of Arabic ethnicity.

Materials and Methods

This study has been approved by the "Human Research Ethical Committee" of Ninevah Health Directorate, Ninevah, Iraq in April 2013. Written consents were obtained from all participants after explaining the research objectives, plans and procedures during a brief interview and the work was conducted by the ethical standards of Declaration of Helsinki II.

This age, sex and ethnicity matched case-control study was designed to investigate the association of the Pro12Ala mutation of *PPAR-γ* gene with T2DM among 192 adult Iraqi people over a period of 7 months from May 3rd. Through November 30^{th,} 2013. It involved 97 (57males and 40 females) unrelated adult (34-71 years old) Arabic Iraqi T2DM patients with variable duration and onset of diabetes consulting Al-Wafaa Center of Diabetes Care and Education in Western Mosul, Ninevah, Iraq and 95 (51males and 44 females) apparently healthy unrelated non-diabetic Iraqi adult (30-70 years old) subjects with negative family history of diabetes mellitus.

Diabetes mellitus was defined by physician's diagnosis according to the American Diabetes Association (ADA) criteria; a fasting plasma glucose (FPG) level ≥ 7 mmol/l (126 mg/dl), two hours postprandial glucose (2h PG) level ≥ 11.1 mmol/l (200 mg/dl) or use of diabetes medications [29]. Iraq is a multi-ethnic, multi-religious and multi-nationalities country. This study focused only on Arabic residents of different urban areas of Mosul City, Ninevah Province, Northern Iraq without a history of mixed marriages with other ethnicities till the third generation.

The diabetic patients who formed Group (I) were recruited for history taking, physical examination and blood collection, when ready, after overnight fasting. Resting blood pressure was measured in sitting position, and anthropometric measurements were taken including height and weight with shoes off and light clothes. Body mass index (BMI) was calculated as weight (kg)/ height (m)^2. Patients were excluded from the study when having T1DM, previous history of ketoacidosis, other than Arabic ethnicities, history of liver or kidney diseases (or any malignancy) or being involved in another clinical or interventional study.

The subjects who formed Group (II) were basically the relatives of non- diabetic patients admitted for surgical operations at Al-Joumhori Teaching Hospital in Western Mosul in addition to the

members of the nursing staff of the hospital. They have all fulfilled the inclusion criteria and agreed to participate in this study.

To be considered as "Controls", subjects were required to be over the age of 30 years, having a negative personal and family history of diabetes mellitus with their fasting plasma glucose being in the normal range (3.33-5.56 mmol/l) following overnight fasting. Any history of previous abnormal glucose homeostasis and current FPG > 5.56 mmol/l was enough to exclude the subject from the control group. Other exclusion criteria for being among the controls included the history of liver or kidney diseases, history of current or recent participation in an interventional study or drug abuse. History was taken from control subjects; anthropometric parameters were measured, resting blood pressure was recorded, and blood was aspirated.

Plasma glucose was estimated manually at the laboratory of Biochemistry, Mosul Medical College relying on glucose oxidase-peroxidase method, which is highly specific for D-glucose [30] using a kit supplied by Randox Ltd (England). The genetic work has been conducted in the PCR laboratory of Ibn Al-Atheer Teaching Hospital, Eastern Mosul. Genomic DNA was extracted from EDTA-treated whole blood samples using ReliaPrep™ Blood gDNA MiniPrep System (Promega Corporation, USA) following the manufacturer's protocol. All T2DM patients and controls were genotyped for the Pro12Ala of *PPARG* gene using PCR-based restriction fragment length polymorphism (PCR-RFLP) assay as designed by Hamann *et al.* [31]. A 306 bp DNA sequence embracing the ambiguity site (**c**ca→**g**ca) at codon 12 was first amplified using primers supplied by (GenScript, USA) as forward:

5′-GCCAATTCAAGCCCAGTC-3′

and reverse:

5′-CGTCCCCAATAGCCGTATC-3′

Amplification was done over 35 cycles in a final volume of 25 µl using 12.5 µl of 2XQiagen's PCR Master Mix (containing $MgCl_2$ at final concentration of 3mM and 5 units/µL HotStar Taq *Plus* DNA polymerase), 0.5 µl of each of forward and reverse primers (10 µM), 9µl of RNase- free water and 2.5 µl (average 300 ng) of DNA. The thermal conditions used for the amplification of the rs1801282 in our subjects are shown in Table 1.

Table 1: Thermal conditions to amplify Pro12Ala for subsequent RFLP

CONDITION	TEMPERATURE	TIME
Initial denaturation	95˚C	5 min
Denaturation	95˚C	30 sec
Annealing	60˚C	90 sec
Extension	72˚C	30 sec
Final extension	68˚C	10 min
Final volume= 25 µl, cycles= 35		

Following PCR, amplicons (306 bp) were subjected to digestion by a specific restriction endonuclease where the C/G variation creates a restriction site for *HgaI* enzyme. The recognition site for *HgaI* is the following:

5′- G A C G C (N) 5 ▼..3′

3′- C T G C G (N) 10 ▲..5′

Ten-µl of PCR products were digested with 3 units of HgaI (New England Biolabs, UK) in a total reaction volume of 50 µl containing 5 µl of 10X 1.1 NEBuffer (10 mM Bis Tris Propane-HCl, 10 mM $MgCl_2$, 1 mM dithiothreitol, pH 7.0 at 25°C) at 37C° for 60 minutes. The reaction was terminated by enzyme inactivation at 65°C for 20 min. DNA fragments were separated on 2% agarose gel stained with SYBR ® Safe DNA Gel Stain (Promega, USA) following standard gel electrophoresis, visualised on the UV transilluminator and photographed. Control DNA samples (wild-type CC, heterozygous mutant CG and homozygous mutant GG) whose genotypes were already confirmed by sequencing (primer extension) were subjected to the same PCR_RFLP reactions, and their digestion products were used in the electrophoretic runs for the confirmation of the samples genotypes.

Statistical Analysis

Standard statistical methods were used to determine the mean, standard deviation (SD) and range (minimum-maximum). One Sample Kolmogorov- Smirnov Test (two-tailed) was used to investigate the normality of distribution of the study variables. Two-tailed unpaired Student's t-test was used to compare the mean values of continuous variables among subjects in different groups when variables were normally distributed or otherwise replaced by Mann Whitney-U test to compare variables that did not follow the normal distribution pattern.

Categorical variables were compared by Chi-square (χ^2), or by using Fisher's exact test if the number of observations within a cell was less than five. Obedience of Pro12Ala genotypes to the Hardey-Weinberg Equilibrium (HWE) was also assessed using χ 2 test. HWE calculator was obtained from http://www.tufts.edu. Logistic regression analysis was used to study the relation between T2DM as the dependent variable and other influencers (like Pro12Ala gene polymorphism) as the independent variables. Mantel- Hanszel test was used to calculate the Odd's ration for the association of Pro12Ala with T2DM and its 95th CI. Differences between observations were considered non- significant at p > 0.0.5. Analyses were carried out using the Statistical Package for the Social Sciences (SPSS Statistics, 17.0).

Results

Among the diabetic patients, using the One-Sample Kolmogorov-Smirnov test, the age, body weight, BMI, systolic blood pressure (SBP) and FPG were normally distributed ($p > 0.05$). However, diastolic blood pressure (DBP) did not follow the pattern of normal distribution ($p < 0.05$). On the other hand, however, both SBP and DBP were not normally distributed among the controls. The results of One-Sample Kolmogorov-Smirnov Test for the characteristics' distribution of both diabetics and controls are displayed in Table 2.

Table 2: The pattern of distribution of the basic characteristics of subjects in both study groups using One- Sample Kolmogorov- Smirnov test.

		Age (years)	Weight (kg)	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)	FPG (mmol/l)
Diabetics (Group I) (n = 97)	Mean	53.42	81.56	30.14	130	81	9.78
	SD	7.55	11.48	4.87	22	12	3.59
	Kolmogorov-Smirnov Z-value	1.06	0.73	0.69	1.04	1.65	1.10
	p-value	0.22	0.66	0.73	0.23	0.01*	0.18
Non-diabetics (GroupII) (n = 95)	Mean	51.04	74.48	27.73	124	81	4.41
	SD	8.00	17.04	6.22	16	8	0.59
	Kolmogorov-Smirnov Z-value	1.27	0.81	0.73	2.64	2.60	0.67
	p-value	0.08	0.52	0.67	<0.0001*	<0.0001*	0.76

BMI: body mass index; SBP: systolic blood pressure; DBP; diastolic blood pressure; FPG: fasting plasma glucose; SD: standard deviation. *p < 0.05 using One Sample Kolmogorov-Smirnov Test (two-tailed) indicates that variables are not normally distributed.

The variables that were not normally distributed in either group of subjects were transformed to their Log10-values, and the One-Sample Kolmogorov Smirnov Test was repeated one more time. Log10 transformation did not succeed to normalize DBP and SBP values ($p < 0.0001$).There were no statistically significant differences in the mean age, sex distribution, smoking frequency and DBP between the two groups ($p > 0.05$ for all). Non-diabetic controls demonstrated significantly lower mean values of body weight, BMI, FPG and SBP (Table 3).

Table 3: The basic clinical, anthropometric and biochemical characteristics of the diabetic and control subjects

Parameter		Group I (T2DM patients) (n= 97)	Group II (Control subjects) (n = 95)	p-Value
		mean ± SD or n (%)	mean ± SD or n (%)	
Age (years)		53.42 ± 7.55	51.04 ± 8.00	0.05
Sex	Males	54 (55.67)	51 (53.68)	0.40
	Females	43 (44.33)	44 (46.32)	
Body weight (Kg)		81.56 ± 11.48	74.48 ± 17.04	0.001
BMI group (Kg/m^2)	< 25	14 (14.44)	37 (38.94)	<0.01
	25-30	35 (36.08)	25 (26.32)	
	> 30	48 (49.48)	33 (34.74)	
BMI (Kg/m^2)		30.14 ± 4.87	27.73 ± 6.22	0.003
Hypertension	Yes	60 (61.86)	35 (36.84)	<0.001
	No	37 (38.14)	60 (63.16)	
SBP (mmHg)*		130.2 ± 22.8	124.9 ± 16.3	0.04
DBP (mmHg)*		81.3 ± 12.3	81.1 ± 8.67	0.63
Smoking	Yes	44 (45.36)	32 (33.68)	0.09
	No	53 (54.64)	63 (66.32)	
FPG (mmol/L)		9.78 ± 3.59	4.41 ± 0.59	<0.0001

* Using Mann Whitney-U test. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose. Hypertension was defined by having SBP≥ 140 mmHg and DBP ≥ 90 mmHg or use of antihypertensive drugs.

Genotypes frequencies of Pro12Ala (rs1801282) among diabetic subjects and controls were within HWE [(χ2=0.35, p= 0.554) and (χ 2=1.04, p= 0.308)] respectively. The comparisons of the allelic and genotypic frequencies of Pro12Ala mutation of PPAR-γ2 gene between diabetics and controls did not show any statistically significant differences [(χ^2= 1.99, p= 0.16) and (χ^2= 2.17, p= 0.14)] respectively (Table 4).

Table 4: Comparisons of allelic and genotypic frequencies of "Pro12Ala" polymorphism among diabetics and controls

	Allelic Frequency n (%)		Genotypic Frequency n (%)		
	C (Pro)	G (Ala)	CC (Pro/Pro)	GC (Pro/Ala)	GG (Ala/Ala)
Diabetic Patients (Group I) N = 97	183 (94.33)	11 (5.67)	86 (88.66)	11 (11.34)	0 (0.00)
Non- Diabetics (Group II) N = 95	172 (90.53)	18 (9.47)	77 (81.05)	18 (18.95)	0 (0.00)
p- value*	0.16		0.14		

*Using Chi-square test.

The association of the mutant allele of the Pro12Ala polymorphism with T2DM was assessed using logistic regression analysis where diabetes was assigned as the dependent variable while Pro12Ala, age, sex, BMI and smoking were considered as the independent co-variables. The analysis demonstrated that having the Ala12 allele is not associated with T2DM (B= -0.16, P= 0.74). However, age, BMI and smoking were significantly associated with the development of diabetes in the study subjects (Table 5).

Table 5: Logistic regression analysis for the association of Pro12Ala mutation of *PPAR-γ* gene and other co- variables with T2DM

Factor	B- value	p- value
Pro12Ala gene variant	-0.16	0.74
Age	-0.03	0.04
Sex	0.02	0.63
BMI	-0.04	< 0.01
Smoking	-1.03	0.02

*BMI: body mass index. The fitness of model was assessed by R- square estimation (R^2 was 0.45) and by Hosmer and Lemeshow test (χ^2= 13.11, df=8, p-value= 0.11).

The Odds' ratio and its 95% confidence interval (95 % CI) for the association of Pro12Ala mutation with T2DM were calculated using Mantel-Haenszel test. The Pro12Ala was not associated with the risk of developing T2DM where Odd's ratio was 0.55 (95% CI= 0.23-1.32, p= 0.14).

The presence of the Ala12 allele was not associated with any significant differences in the mean values of body weight, FPG, SBP, DBP and BMI in both diabetics and non- diabetic subjects (p> 0.05 for all). However, the Pro12Ala mutation was more prevalent among male non- people with diabetes compared to females in the same group (77.78% vs. 22.22%, p= 0.02). The genotypes distribution by BMI did not show significant differences between Pro/Pro and Pro/Ala carriers in the presence and absence of T2DM (p= 0.91 and 0.72 respectively)

(Table 6).

Discussion

The CCA to GCA variation at codon 12 of the *PPAR-γ2* specific exon is a common sequence variation with a reduced functional capacity as a transcriptional factor for a large number of genes [21], [32]. The minor allele frequency of the Pro12Ala polymorphism of the PPAR-γ gene has found to vary widely across different populations worldwide with its lowest frequency being in people of East Asian descent and highest figures being in Caucasians [22]. In Iraq, and to best of our knowledge, this is the first study that investigates the distribution and the association of this common functional polymorphism with T2DM among adult Iraqi subjects of Arabic descent. Iraq is a multinational and a multi-ethnic country in North-West Asia. This study has focused on a populations' sample of 192 non- related Native Arabic adult Iraqis living in urban areas of Mosul, the biggest city of Ninevah Province which is the second largest province in Iraq.

Table 6: Comparisons of clinical, anthropometric and biochemical variables of people with diabetes and non- people with diabetes by their genotypes of Pro12Ala mutation

		Diabetics (Group I) (n = 97)			Non- Diabetics (n = 95)		
		Pro/Pro (n = 86)	Pro/Ala (n = 11)	p-value	Pro/Pro (n = 77)	Pro/Ala (n = 18)	p-value
Sex	Female	36 (41.9)	7 (63.64)	0.17	40 (51.9)	4 (22.22)	0.02
	Male	50 (58.1)	4 (36.36)		37 (48.1)	14 (77.78)	
Body weight (Kg)		82.06± 11.71	77.64± 8.97	0.16	75.28± 10.22	74.29± 18.32	0.76
BMI (Kg/m^2)		30.23± 5.05	29.40± 3.12	0.41	27.76± 6.56	27.55± 4.54	0.80
BMI Groups	< 25	12 (85.71)	2 (14.29)	0.91	30 (81.08)	7 (18.92)	0.72
	25- 30	31 (88.57)	4 (11.43)		20 (76.92)	6 (23.08)	
	≥ 30	43 (89.58)	5 (10.42)		27 (84.38)	5 (15.62)	
SBP (mmHg)		129.9± 23.0	132.3± 21.5	0.60	124.9± 16.9	125± 13.9	0.78
DBP (mmHg)		81.4± 12.6	80.9± 9.7	0.97	81.0± 8.9	81.7± 7.9	0.82
FPG (mmol/l)		9.87±3.66	9.11± 3.09	0.40	4.51± 0.60	4.35± 0.53	0.62

*Values are expressed as mean ± SD or n(%). Comparisons of continuous variables were made using unpaired Student's t-test (two-tailed) except for SBP & DBP which were compared using Mann Whitney U test. Sex distribution was assessed by Chi-square test while genotypes distribution by BMI was compared by Fisher's Exact test.

We demonstrated lack of statistically significant differences in the allelic and genotypic frequencies of Pro12Ala mutation between diabetic patients and non- diabetic controls. The Odd's ratio of the association between diabetes and this mutation was not significant (p = 0.14). Moreover, the Pro12Ala polymorphism of the human *PPAR gamma* gene was not a significant independent factor in the aetiology of T2DM in our patients (p = 0.74).

These results point towards lack of association between the mutant *PPAR-γ2* gene variant and the development of T2DM among the studied sample of the Iraqi population. Similar to the findings of the current study, other researchers have also revealed no evidence of an association between Pro12Ala and diabetes among different European and Asian populations [33] [34] [35].

Reports from our region, the Middle East, also showed this lack of association between diabetes and Pro12Ala. Among these is a study of Tunisian subjects by Zouari Boussaida *et al.* [26]. Also, in Qatar, Badii *et al.* have found that the frequency of the mutant allele of Pro12Ala among cases of T2DM did not differ significantly from that of controls and that the association of this polymorphism with diabetes was not significant among Qatari consanguineous population [36].

Several previous studies elsewhere have demonstrated a significant association of the Pro12Ala polymorphism with T2DM. Ghoussaini *et al.* found a significant association between PPAR-γ 2 Pro12Ala variant and T2DM [37]. The Pro12Ala polymorphism of *PPARG* gene contributed to the risk of developing T2DM in 554 Indian Sikhs according to a recent study [38]. More recently, a study in 2012 revealed that genetic variants of *PPAR-γ, ADIPOQ* and *HNF4A* genes were individually and jointly associated with T2DM among Hong Kong Chinese people and that the Pro12 allele is the risk allele for both T2DM and coronary heart disease [39].

Although a few studies only observed a higher Ala12 allele frequency among the diabetic patients compared to healthy controls conferring the possible "risky" contribution of the Ala12 allele, the association of the Pro12 allele of the *PPAR-γ* gene with diabetes mellitus was the basic finding of many other studies worldwide including an extensive meta- analysis involving 3000 individuals which showed a 1.25- fold increase in the diabetic risk upon having the wild-type allele [40] [41] [42] [43] [44] [45] [46] [47] [48].

While the exact mechanisms by which the Pro12Ala variant of *PPAR-γ* gene is associated with diabetes is not fully understood, it seems that the Ala12 allele improves the peripheral insulin sensitivity by reducing the release of insulin-desensitizing free fatty acids, tumor necrosis factor-alpha and resistin in addition to the increased release of adiponectin (an insulin-sensitizing hormone). These effects will ultimately enhance peripheral glucose uptake and inhibit the hepatic glucose production [16].

The inconsistency of the results of different association studies all over the world- including the current work- may be partially explained by the heterogeneity of the participant's ethnicity. It is assumed that around 14% of the between-studies variances may be attributed to differences in the ethnicity [21].

Also, the differences in the allelic and the genotypic frequencies of the Pro12Ala gene variant among different populations, and thus their contribution to the Odd's ratio of this mutation as a predictor for T2DM may also be referred to the possible overestimation or underestimation of the mutations' frequency. Different scientists used

different genotyping techniques to investigate the mutation like PCR-RFLP, TaqMan probes, DHPLC and others which may have different sensitivities. Differences in the study designs and sample sizes may affect the results.

Small sample size in some studies- including this one- may affect the power of the statistical analyses. For this purpose, we conducted a Post- hoc analysis to compute the achieved power of the study using the G*Power software 3.0.10 (Exact- proportions). The power was 0.69 assuming an expected rate of the risky allele (Pro12) to be 0.95 among people with diabetes and 0.85 among controls. Our small sample size, thus, represents a major study limitation that may affect our conclusions regarding the association of the polymorphism with diabetes and its subsequent impact on the diabetic phenotypes in our patients.

Other possible influences that perhaps stand behind these discrepancies may be possible gene-gene interactions and some gene-environmental (including gene-diet) interactions. Controls chosen to participate in many of the association studies including the current one may not have been selected so perfect. So many of these studies relied on self-reported controls with random glucose measurement to rule out diabetes. A better controls selection would probably require conducting oral glucose tolerance test (OGTT).

These divergent results may also be explained by the possible effect of the Pro12Ala gene variation on other factors that contribute to the aetiology of diabetes like insulin secretion and/or action in response to free fatty acids and physical activity [49] [50]. People in our community are consuming a lot of fat in their diet and are currently experiencing a more westernised pattern of life than before with overtly reduced average daily physical activity. These interactions may attenuate the susceptibility to diabetes in the presence of the less risky Ala12 allele. For this reason, we highly recommend emphasising on having detailed information on diet and physical activity measures in parallel with the Pro12Ala mutation analyses in Iraqi people in the future investigations.

PPAR-γ2 gene variant plays important roles in the adipocytes differentiation and energy metabolism. Its variants like Pro12Ala substitution are expected to be associated with obesity [51]. Our subjects carrying the Ala allele, whether diabetics or controls, got lower mean body weight and BMI respectively than those carrying the wild-type allele only although these comparisons did not reach the level of statistical significance.

In our study, the differences in the frequency of the Ala12 allele by the BMI categories were not statistically significant and in comparison to lean subjects, obese subjects did not demonstrate a statistically significant lower frequency of the mutant allele (p = 0.74). Wang *et al.* indicated that the Pro12Ala variant of the *PPAR-γ* gene is associated with obesity in Chinese Han people. Their diabetic and non- diabetic carriers of Ala12 carriers were significantly leaner than non- Ala12 carriers. However, they demonstrated that the frequency of the Ala12 allele was significantly lowest at BMI> 28 kg/m^2 [44].

Again the variance in the sample size (192 vs 3146) can partially explain this inconsistent association of Pro12Ala gene polymorphism with obesity in both studies. Another reason can be the different definitions of obesity adopted by the two studies where our study relied on the BMI cut points by WHO [52] which are basically derived from data of Western population, while Wang *et al.* considered obesity at BMI≥ 28 kg/m^2 and overweight at BMI ≥ 24 kg/m^2. Asians may have more cumulative risks for the development of cardiovascular diseases at these lower BMI values [53] [54].

Despite that the current work demonstrated a lower mean BMI among (Ala) allele carriers with and without diabetes mellitus, there are some reports that non- diabetic carriers of the mutant allele of Pro12Ala gene variant may have a higher tendency to gain weight over time [36], [55]. Lindi *et al.* demonstrated that carrying the Ala12 allele would be rather in favour of increased insulin sensitivity and thus weight gain happens without the development of diabetes. In our study, the lower mean fasting glucose level among the diabetic and the non- diabetic heterozygotes compared to the wild-type homozygotes may reflect this improved insulin sensitivity and supports this hypothesis. However, direct measurement of insulin sensitivity (as by IVOGTT or hyperinsulinaemic euglycemic clamp) or its surrogate measurements (like by HOMA, or QUICKI) would better affirm this.

PPAR-γ is an important player in blood pressure control [10]. In our study, the Pro/Ala heterozygotes demonstrated a higher mean value of SBP compared to the Pro/Pro homozygotes although this relation has not been adjusted for other independent risk factors like age and BMI as this comparison did not reach the level of significance. By our results, other investigators have demonstrated an association between the Ala12 allele and the elevation of systolic blood pressure and/or diastolic blood pressure [56] [57]. A reasonable explanation for this association between hypertension and Pro12Ala polymorphism is the one already suggested by Sugawara *et al.* [58] who showed that PPAR gamma activation could downregulate the expression of the angiotensin II receptor gene in the vascular smooth muscle cells among experimental animals. This effect may be abolished when the PPAR-γ protein loses a part of its transcriptional capacity upon having functional polymorphisms in its coding gene as in case of rs1801282.

Our study revealed a relatively high frequency of the Ala12 allele and Pro/Ala genotype of Pro12Ala

polymorphism among Iraqi people of Arabic descent. However, these frequencies were not significantly different among diabetics and non- diabetic control subjects. The Pro12Ala mutation failed to predict T2DM in our subjects and did not behave as an independent risk factor for the development of diabetes possibly due to the limited study power because of the relatively small sample size. However, the risk of diabetes in our patients was evidently related to other independent variables like age, body mass index and smoking. Although non-significant, Ala12 carriers exhibited lower mean body weight and BMI regardless of diabetes. The lower mean blood glucose level among these subjects may reflect higher peripheral insulin sensitivity than what may Pro/Pro carriers have. Also, the Ala12 allele carriers may be prone to systolic hypertension possibly due to the reduced transcriptional capacity of the mutant *PPAR-γ* gene variant.

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Eosinophil Cationic Protein Concentrations among Crop and Dairy Farmers with Asthma

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Abstract

OBJECTIVE: To assess the mean serum eosinophil cationic protein (s-ECP) concentrations among crop and dairy farmers and office controls, and further examine its relation to exposure duration, smoking habit, as well as presence or absence of asthma.

METHODS: A cross-sectional survey was performed including examined group (EG), composed by agricultural workers (87 crop - EG1 and 83 dairy farmers - EG2), and control group (CG) composed by 80 office workers within the same enterprise. We have used a questionnaire to record the chronic respiratory symptoms, detailed work history, specific farming activities and tasks performed and smoking history. Evaluation of examined subjects also included lung function tests, diagnosis of asthma, and measurement of s-ECP as a marker of inflammation.

RESULTS: The main finding of the present study is that s-ECP concentrations were raised in subjects with asthma independent of the smoking habit. The mean s-ECP concentrations were higher in subjects of EG1 and EG2 compared with those in CG, but without reaching statistical significance. Mean s-ECP concentrations were significantly higher among subjects in EG1 exposed more than 20 years, while mean s-ECP concentrations were non-significantly higher in subjects of EG2 exposed more than 20 years, compared to those exposed less than 20 years. Mean s-ECP concentrations were higher among smokers within all three groups, but without reaching statistical significance between smokers and non-smokers. Mean s-ECP concentrations were significantly higher in subjects with asthma within EG1 (P = 0.049) and EG2 (P = 0.040), but also within those in CG (P = 0.046).

CONCLUSION: Data obtained suggest that airway inflammation is present in farmers with asthma, and s-ECP is an important biomarker in means of reflecting disease severity and prognosis among exposed workers.

Introduction

Asthma is a chronic inflammatory disease of the airways in which many inflammatory cells have been found to play a role, particularly mast cells, eosinophils and T-lymphocytes. The association between eosinophilia and asthma was observed shortly after eosinophils were discovered. In patients with asthma, eosinophils are present in increased numbers in the blood, sputum and bronchoalveolar lavage fluid [1].

After activation, eosinophils can release granulocyte-derived proteins, the most toxic of which are eosinophil cationic protein (ECP) and major basic protein (MBP) [2]. Clinical research has suggested emerging clinical usefulness of eosinophil granule proteins as serological markers in the assessment and management of asthma, of which ECP has been most widely characterised and researched. The results of many studies indicate that the degree of eosinophilic expression, that is, the levels of ECP in the blood and serum correlate with the degree of asthma severity and the extent of the achieved asthma control [3].

Immunologically potent substances such as antigens, endotoxins, glucans and substances with

complement-stimulating and adjuvant effect have been identified in the agricultural dust, exposure to which may provoke inflammatory reactions in the airways [4]. In a population study of farmers, lifetime cumulative prevalence of asthma was 6.3%, and for current asthma was 3.1%. Melbostad et al. found that animal production (husbandry) and familial predisposition interact as risk factors for asthma in farmers, and that atopy and specific allergies to cow, swine, grass and mites (*D. pteronyssinus, L. destructor* and *T. putrescentiae*) are associated with asthma and work-related upper and lower airway symptoms [5]. Eosinophil airway inflammation is characteristic of asthma, and, as shown in provocation studies, seems to be related to current asthma activity and recent allergen exposure [6]. Serum ECP value is a relevant marker of current eosinophil inflammatory activity in asthma [7]. There is a need for markers of airway inflammation in epidemiological studies of asthma.

In an epidemiological study of asthma in Norwegian farmers, Melbostad et al. [8] investigated s-ECP values in cases of atopic and non-atopic asthma, respectively, and in a control group without asthma and atopy. They also studied the relationship between airway obstruction, as an indicator of asthma activity, and s-ECP values, and whether ECP values were related to some positive allergen tests and specific allergies in asthmatic farmers.

Activated eosinophils in the asthmatic release their granular proteins, supporting the view that they have a pro-inflammatory role in the development of airway narrowing in asthma [9]. One such protein, ECP, was detected in bronchial biopsies and measured BAL [10], sputum and peripheral blood [11]. Serum and sputum ECP levels have been found to be correlated with the severity of asthma and allergen exposure [12]. It has been found that ECP can be used to monitor asthma inflammation [13].

The Italian study conducted among asthmatic grass-sensitized farmers by Di Gioacchino et al. [14] demonstrates that in grass sensitized farmers with asthmatic symptoms occurring for several weeks after grass pollination has ceased, the degree of airway hyperresponsiveness and the duration of post seasonal symptoms are directly related to the increase of ECP levels during the pollen season, as well as to the level of total IgE in serum. This allows identification of two candidate biomarkers (easily usable in routine clinical practice) for the risk of developing prolonged asthma symptoms, and for the effective monitoring of anti-inflammatory treatment and allergen-specific immunotherapy. The review of the literature indicated that s-ECP might serve as an objective indicator for clinical activity in asthma, and point to a possible pathophysiological axis in asthma that is based upon altered airway resistance due to eosinophils and eosinophil activity markers [15].

In the actual study we have assessed the mean s-ECP concentrations among crop and dairy farmers and office controls, and further examined its relation to exposure duration, smoking habit, as well as the presence or absence of asthma.

Subjects and Methods

Study design and setting

We have performed cross-sectional research in the Center for Respiratory Functional Diagnostics at the Institute for Occupational Health of Republic of Macedonia, Skopje - WHO Collaborating Center for Occupational Health and GA^{2}LEN Collaborating Center within the period September 2014 and April 2015. The examined and control groups are the same cohorts that were used in our previous study [16].

Subjects

The survey included workers employed at agricultural enterprise divided into two groups: examined group (EG), composed by agricultural workers (crop and dairy farmers), and control group (CG) composed by office workers within the same enterprise.

EG consists of 170 subjects, while CG has 80 examinees. For the study purposes, and depending on the main agricultural activity, subjects were divided into two groups, examined group 1 (EG1) and examined group 2 (EG2). EG1 comprised 87 crop farmers (mean age = 53.4 ± 7.8 years) engaged in crop farming (mean duration of exposure 22.9 ± 7.8 years) with main activities composed of cultivating crops and vegetables, planting, digging, use of mechanised equipment, irrigation, and pesticide handling. They were exposed to various respiratory agents: dust, inappropriate climate, fumes, vapours and pesticides. EG2 consists of 83 dairy farmers (mean age = 52.6 ± 8.7 years) employed as dairy farmers (mean duration of exposure 23.7 ± 7.6 years), working inside confinement buildings, and exposed to: dust, inappropriate microclimate conditions, chemical hazards, vapors, gases, heavy manual work, animal contact, unfavorable body positions, and repetitive hand movements. Their main occupational activities were: preparation of fodder feeding and animal meals, milking, staying in the barn, preparation of straw, and haymaking, cattle raising, as well as taking care about milk hygiene and animal health.

Also, a similar group of 80 office workers (mean age = 52.7 ± 8.2 years) with no exposure to respiratory agents, matched for age, duration of employment, daily smoking and socioeconomic status was studied as a control.

The Institute's ethics committee has approved

the content of our study protocol, whereas each examined subject was informed and gave written consent before any involvement in the study.

Questionnaire

All study subjects were interviewed by the standardised questionnaire, including questions on work history, respiratory symptoms in the last 12 months, and smoking habit.

Chronic respiratory symptoms in the last 12 months (a cough, phlegm, dyspnea, wheezing, and chest tightness) were obtained using the European Community for Coal and Steel questionnaire (ECCS - 87), and the European Community Respiratory Health Survey (ECRHS) questionnaire [17] [18]. Classification of smoking status was done according to the World Health Organization (WHO) guidelines on definitions of smoking status [19].

Daily smoker was defined as a subject who smoked at the time of the field survey at least once a day, except on days of religious fasting. Among daily smokers, lifetime cigarette smoking and the daily mean of cigarettes smoked were also assessed. Pack-years smoked were calculated according to the actual recommendations [20]. Ex-smoker was defined as a formerly daily smoker, no longer smokes. Passive smoking or exposure to environmental tobacco smoke (ETS) was defined as the exposure of a person to tobacco combustion products from smoking by others [21].

Spirometry

All study subjects underwent spirometry testing, performed by spirometer Ganshorn SanoScope LF8 (Ganshorn Medizin Electronic GmbH, Germany), measuring forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, and maximal expiratory flow at 50%, 75%, and 25–75% of FVC (MEF_{50}, MEF_{75}, and MEF_{25-75}, respectively), by recording the best result from three measurements of the values of FEV_1 within 5 % of each other. The results were expressed as percentages of the predicted values according to the European Community for Coal and Steel (ECCS) norms [22].

Diagnostic criteria for asthma

According to the actual recommendations by Global Initiative for Asthma (GINA) asthma in subjects with normal spirometric findings is defined as symptomatic bronchial hyperresponsiveness (BHR) with $PC_{20} \leq 4$ mg/mL, while in those with lower values of spirometric parameters as a positive bronchodilator test [23].

Measurement of s-ECP concentrations as markers of inflammation

Mean s-ECP concentrations are measured by chemiluminescent immunoassay method with Immulite 1000 in subjects with chronic respiratory symptoms and spirometric impairment. s-ECP concentrations < 24 µg/L are within the normal range [24].

Statistical analysis

We have analysed the data using Statistica for Windows version 7. Continuous variables were expressed as mean values with standard deviation and categorical variables as numbers and percentages. The comparison of mean ECP serum concentrations was performed by independent-samples T-test. A P-value of less than 0.05 was considered statistically significant.

Results

Table 1 gives an overview of the demographic and overall characteristics of the subjects within the examined and control groups.

Table 1: Demographic and overall characteristics of the study subjects

Variable	EG1 (n = 87)	EG2 (n = 83)	CG (n = 80)
Gender/M/F ratio	3.6	2.6	2.7
Age/years	53.4 ± 7.8	52.6 ± 8.7	52.7 ± 8.2
BMI/ kg m^{-2}	25.1 ± 3.5	25.4 ± 3.6	26.2 ± 3.7
Duration of employment / years	29.2 ± 8.9	26.3 ± 10.1	25.3 ± 9.8
Exposure duration / years	22.9 ± 7.8	23.7 ± 7.6	/
Active (daily) smokers	45 (51.7%)	39 (46.9%)	39 (48.7%)
Smoking experience/years	19.7 ± 8.1	18.9 ± 7.6	19.2 ± 7.8
Cigarettes / day	15.4 ± 7.3	14.6 ± 6.8	14.8 ± 7.2
Ex-smokers	12 (13.8%)	9 (10.8%)	12 (15%)
Passive smokers	11 (12.6%)	8 (9.6%)	7 (8.7%)

Numerical data are expressed as mean values with standard deviations; frequencies of active, passive, and ex-smokers are given as number and percent of subjects with certain variable.M: males; F: females; BMI: body mass index.

Table 2 shows the frequencies of asthma symptoms (a cough, dyspnea, wheezing and/or chest tightness), positive BD tests, positive non-specific histamine challenge tests with $PC_{20} \leq 4$ mg / mL, as well as asthma detected among subjects in EG1, EG2 and CG.

Table 2: Frequency of asthma symptoms, positive BD tests, positive histamine challenge tests with $PC_{20} \leq 4$ mg/mL, and asthma among subjects in EG1, EG2 and CG

Variable	EG1 (n = 87)	EG2 (n = 83)	CG (n = 80)
Respiratory symptoms in the last 12 months	26 (29.9%)	24 (28.9%)	16 (20%)
Positive BD test	15 (17.2%)	14 (16.9%)	8 (10%)
Positive histamine challenge test with $PC_{20} \leq 4$ mg/mL	9 (10.3%)	7 (8.5%)	5 (6.3%)
Asthma	7 (8%)	6 (7.2%)	4 (5%)

Data are given as number and percent of subjects with a certain variable.

For the study purposes, we have examined

the marker of chronic eosinophil inflammatory activity-s-ECP among subjects in the three groups having one or more chronic respiratory symptoms and / or spirometric impairments.

Determination of mean s-ECP concentrations

The mean s-ECP concentrations were higher in EG1 compared to CG, but without statistical significance (Table 3).

Table 3: Mean s-ECP concentrations in subjects of EG1 and CG

	EG1 (n = 35)	CG (n = 15)	*P*-value*
s-ECP (μg/L)	14.4 ± 3.7	12.6 ± 3.2	0.108

Data are given as means with standard deviation. * Tested with t-test for independent samples.

Mean s-ECP concentrations were higher in subjects of EG2 compared to those of CG, but statistical significance is not yet reached (Table 4).

Table 4: Mean ECP serum concentrations in subjects of EG2 and CG

	EG2 (n = 32)	CG (n = 15)	*P*-value*
s-ECP (μg/L)	13.9 ± 3.5	12.6 ± 3.2	0.229

Data are given as means with standard deviation.* Tested with t-test for independent samples.

Table 5 shows the mean s-ECP concentrations in subjects of EG1 with exposure duration less or equal to 20 years and over 20 years.

Table 5: Mean ECP serum concentrations in subjects of EG1 according to job exposure duration

	Exposed > 20 years (n = 24)	Exposed ≤ 20 years (n = 11)	*P*-value*
s-ECP (μg/L)	16.2 ± 4.3	13.1 ± 3.1	0.039

Data are given as means with standard deviation.* Tested with t-test for independent samples.

Mean s-ECP concentrations were significantly higher in subjects of EG1 exposed more than 20 years, compared to those with job exposure less than 20 years.

Table 6 gives an overview of mean s-ECP concentrations in subjects of EG2 with duration of exposure less or equal to 20 years and over 20 years.

Table 6: Mean s-ECP concentrations in subjects of EG2 according to job exposure duration

	Exposed > 20 years (n = 22)	Exposed ≤ 20 years (n = 10)	*P*-value*
s-ECP (μg/L)	15.1 ± 3.9	12.6 ± 3.2	0.086

Data are given as means with standard deviation.* Tested with t-test for independent samples.

Mean s-ECP concentrations were higher in subjects of EG2 exposed longer than 20 years compared to those with a shorter period of job exposure but without statistical significance.

The mean s-ECP concentrations in subjects of all 3 groups depending on the smoking habit are given in Table 7.

Table 7: Mean s-ECP concentrations in subjects of EG1, EG2, and CG depending on smoking habit

Variable	EG1 (n = 35) 21 vs 14	*P**	EG2 (n = 32) 19 vs 13	*P**	CG (n = 15) 9 vs 6	*P**
s-ECP in active smokers	15.5±4.1	0.208	14.9±3.8	0.107	13.7±3.6	0.664
s-ECP in non-smokers	13.8±3.4		12.7±3.5		12.9±3.1	

Data are given as means with standard deviation.* Tested with t-test for independent samples.

The mean s-ECP concentrations were higher in smokers within the three groups, but without significant difference between smokers and non-smokers.

Mean s-ECP concentrations in all three groups due to the presence or absence of asthma are shown in Table 8.

Table 8: Mean s-ECP concentrations in subjects of EG1, EG2, and CG due to the presence or absence of asthma

Variable	EG1 (n = 35) 7 vs 28	*P**	EG2 (n = 32) 6 vs. 26	*P**	CG (n = 15) 4 vs. 11	*P**
s-ECP in subjects with asthma	18.9 ± 7.5	0.013	17.2 ± 6.9	0 .039	16.8 ± 4.9	0.046
s-ECP in subjects without asthma	13.6 ± 3.8		12.9 ± 3.7		12.1 ± 3.2	

Data are given as means with standard deviation. * Tested with t-test for independent samples.

The mean s-ECP concentrations were significantly higher in subjects with asthma compared to non-asthmatics in all three groups.

Discussion

The average s-ECP concentrations were higher in subjects within EG1 and EG2 compared to those in CG, but without statistical significance. The average s-ECP concentrations were significantly higher among subjects in EG1 exposed more than 20 years, compared to those with exposure less than 20 years, while average s-ECP concentrations were non-significantly higher in subjects of EG2 exposed more than 20 years, compared to those exposed less than 20 years. The average s-ECP concentrations were higher among smokers within all three groups, but without reaching statistical significance between smokers and non-smokers, whereas they were significantly higher in asthmatic subjects compared to those without asthma in all three groups. Similar

results were obtained in the study of Heldal et al. [25] dedicated to occupational exposure to bio-aerosols while ECP as a marker of chronic airway inflammation was confirmed in the research conducted by Hamed et al. focused on the it's predictive value in subjects with poorly controlled asthma and therapeutic response to inhaled corticosteroids [26].

Substantial research work has been carried out to determine changes in s-ECP levels due to different allergic and non-allergic diseases over the last decades and especially during last two decades. As a result of these studies, enough quality work is now available to bridge the link between eosinophil activity and allergy phenomenon. Serum ECP is now closer to be declared as an established marker of allergy [27]. Many reported studies demonstrate an increase in s-ECP concentrations in asthmatic patients as compared to healthy controls [28][29]. Amongst the notable studies of eosinophil activity markers in induced sputum two studies found that ECP levels were significantly positively correlated with the mean weekly total symptom scores [30].

The concentration of serum ECP has recently been found to correlate with ECP concentration in bronchoalveolar lavage fluid (BALF) [31]. Therefore, assessment of s-ECP may be considered to reflect pulmonary inflammation in asthma [32]. Studies of asthmatic patients, especially adults, have indicated a relationship between the level of serum ECP and the severity and nature of the disease [33][34]. The present study showed that the s-ECP levels were significantly elevated in asthmatic subjects as compared to that of healthy controls. This indicated the role of eosinophilic inflammation in the pathogenesis of asthma. It is clear that our results were consistent with previous studies that have shown that higher ECP levels in the serum of asthmatic patients when compared with healthy subjects [33] [34] [35]. Measuring of s-ECP levels have the advantages over eosinophilic count in that it reflects not only the number of cells but also their degree of activation and is, therefore, a better inflammatory marker [35]. The present study results show significant higher s-ECP levels in asthmatic subjects than those without asthma, regardless of the occupational exposure to respiratory hazards. Other studies [29] [34] [36] reported the same association between s-ECP levels and asthma severity.

Thus assessment of s-ECP may be a reflection of pulmonary inflammation in bronchial asthma [37]. The presence of eosinophilic inflammation seems to be of importance since this feature is inconsistently observed in non-asthmatic atopic patients and absent in patients with a chronic cough [38]. Furthermore, these results indicate that although eosinophils are recruited in intermittent asthma, they are less activated in persistent asthma. The different patterns of eosinophilic activation found in persistent as compared with intermittent asthma might be important consequences of the integrity of the bronchial mucosa [39].

Direct measurement of airways inflammation using biological markers could potentially refine asthma management. This explains the current research interest in measuring levels of exhaled nitric oxide and eosinophil granule proteins especially s-ECP in asthma [40]. The study by Zedan et al. [41] revealed that both peripheral eosinophil count and s -ECP levels were significantly higher in atopic asthmatics as a group than in healthy control subjects. On the other hand, both parameters were significantly higher among partially controlled asthma cases compared with healthy control children as well as controlled asthma cases. Interestingly, however, controlled asthma cases showed non-significant changes in the levels of both parameters versus healthy control children. This finding is supported by the evidence that eosinophils play an important role in the pathogenesis of asthma and that elevation of peripheral blood eosinophil count is a risk factor for the development of airway remodelling and irreversible changes in lung function [42]. This is also supported by the research of Lee et al. who reported that higher levels of s-ECP were associated with more severe exacerbation of asthma followed by a decrease in s-ECP levels with a resolution of symptoms [43].

Zedan et al. also showed a significant inverse correlation between the level of asthma control and both parameters, particularly s-ECP, implying that poorer control is expected with higher s-ECP levels [41]. This will add to the work of Koh et al., who described a correlation between asthma severity and s-ECP level. Thus, considering that s-ECP has been widely investigated as a potential biomarker of airway inflammation, it may have a useful role to play as a control parameter in asthma guidelines [2]. Mean s-ECP values were significantly higher in cases of current allergic asthma than in non-allergic asthma, and lowest in non-asthmatic, non-atopic controls. In atopic asthmatics, ECP showed significant associations with airway obstruction and numbers of RAST allergens positive, as well as specific allergies, e.g. to swine and D. pteronyssinus [44]. Serum ECP is not a discriminating test for identifying asthma in epidemiology but can be used as a supplement to questionnaires and spirometry to indicate current asthma activity [42].

The results of a recent study in our country showed that the ICS objectively suppress the inflammatory reaction in asthma and the biologic markers (IL-5, Eo and s-ECP), which if being followed, can measure the accomplished effect. Therefore, they could be used in everyday practice, not only as diagnostic parameters but also as valid therapeutic guides in the treatment of asthma [45]. Another similar research showed that eosinophils, s -ECP and IL-5 could be useful markers for selecting allergic patients and could be the monitors of treatment effects [46]. Assessing eosinophilic inflammation is therefore

important in establishing a diagnosis, in monitoring and assessing response to treatment, and in testing novel therapeutics. Clinical markers of atopy and eosinophilic inflammation include indirect tests such as lung function, exhaled breath condensate analysis, fractional exhaled nitric oxide, serum immunoglobulin E levels and serum periostin. Direct measures, which quantify but do not anatomically localise inflammation, include blood eosinophil counts, serum or plasma eosinophil cationic protein and sputum eosinophil levels. Cytology from bronchoalveolar lavage and histology from endobronchial and transbronchial biopsies are better at localising inflammation but are more invasive. Novel approaches using radiolabelled eosinophils with single-photon emission computed tomography offer the prospect of non-invasive methods to localise eosinophilic inflammation [47].

Our present study has some limitations. Namely, relatively small number of the subjects in the study groups may be a limitation, with possible implications on the data obtained and its interpretation, especially having in mind their extrapolation on the population level for the agricultural workers in the Republic of Macedonia. There is a lack of ambient monitoring and exposure measurement (endotoxin, dust, gases, vapours, and chemicals) in this survey. On the other hand, the data concerning exposure to respiratory hazards are based on job exposure matrices, introduced in our country. Finally, we can confirm that s-ECP is an important biomarker of airway inflammation present among farmers with asthma in means of reflecting disease severity and its prognosis. Furthermore, s -ECP levels were raised independently of smoking status in asthmatic subjects showing that s-ECP rise was a result of the inflammatory nature of the disease itself.

In conclusion, despite the small sample size, this study has demonstrated that s-ECP may have clinical usefulness in assessing levels of asthma control and hence in refining asthma management. Based on these findings, our recommendation is conduction of a larger, randomized controlled trial to evaluate the correlation between s-ECP level and degree of asthma control, in order to obtain a cut-off point for s-ECP beyond which farmers with asthma may be considered uncontrolled, and to extrapolate this point on the population level among agricultural workers, having in mind exposure duration and its characteristics in farming, as well.

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Clinical Science

Carotid Endarterectomy in Women versus Man: Patient Characteristics and Perioperative Complication (<30 Day)

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Abstract

AIM: Compare the basic characteristics of patients and to examine the existence of higher rates of perioperative complications (0 - 30 days) in women versus men after carotid endarterectomy (CEA).

METHODS: This is a retrospective-prospective study included 270 patients with significant stenosis of carotid in whom CEA was performed, during the period from 2012 to 2017. Patients they were divided: group 1 - 100 female patients, group 2 - 170 male patients.

RESULTS: No statistically significant age difference was observed between the two groups, group 1 - 66.01 years (SD 8.42, 46 to 86 years), group 2 - 66.46 years (SD 8.03, 47 to 85 years) (p = 0.659). Risk factors represent a greater prevalence in group 2, but the observed difference is not statistically significant. The average duration of surgery and the time of carotid artery clamping time were longer in group 1: (p = 0.002; p = 0.005). The number of classic endarterectomy with the patch was higher in women (41 (41%) versus 31 (18. 2%), p = 0.005), while the number of bilateral CEAs was not statistically significant.

CONCLUSION: The results of this study of this study did not indicate a greater presence of perioperative complications (< 30 days) in women versus male patients after CEA.

Introduction

Cerberovascular insult (CVI) is the third most common cause of death in industrialized countries, the most common neurological diagnosis requiring hospitalization [1] and the leading cause of disability in the world [2[[3], while not all CVI - s are caused by atherosclerotic carotid artery disease (stenosis, occlusion).

After the first carotid endarterectomy (CEA) performed by De Bakey, the method was established as a safe and effective way to reduce the risk of CVI in patients with critical stenosis of carotid arteries. Today, CEA is a surgical method with low mortality and acceptable incidence of perioperative complications (30 days) in most centres dealing with this issue [4] [5]. Also, the superiority of surgical treatment in patients with symptomatic [6] and asymptomatic carotid artery stenosis is well known [5] [7]. CEA can cause severe perioperative complications (i.e. stroke, death). It is presumed that women may have an increased risk of perioperative complications and that this risk may negate the overall benefit of the procedure in women, particularly in lower - risk subgroups with medicament therapy for stroke prevention. Current literature provides contradictory evidence of CEA risk in women compared to men. Some studies point to a higher

rate of perioperative complications in women [8] [9] [10], while others found no difference between women and men [6] [11] [12] [13] [14] [15] [16].

The study aimed to compare the basic characteristics of patients and to examine the existence of higher rates of perioperative complications (0 - 30 days) in women versus men after CEA.

Patients and Methods

This was a retrospective-prospective observational clinical cohort study conducted in the period from January 2012 to October 2017. Patients with stenosis of carotid arteries in whom CEA was performed at the Clinical Center of the University of Sarajevo were included.

Depending on the sex of the patients were divided into two groups: group 1, consisting of 100 female patients, group 2 - consisting of 170 male patients. The preoperative risk factors were compared between the two groups: hypertension (HTA), hyperlipidemia (HLP), smoking, diabetes mellitus (DM), non - surgical coronary artery disease (CAD) as well as demographic factors, significant stenosis of carotid arteries, the presence of preoperative neurological symptomatology (vertigo, transient ischemic attack (TIA), amaurosis fugax and small CVI). From the perioperative results, the total duration of the operation (time from the first surgical incision to the last suture expressed in minutes), the length of clamping of internal carotid artery (ICA) (expressed in minutes), prosthetic material used in closing the arteriotomy in the classical endarterectomy as well as the history of contralateral side CEA. Of the perioperative complications (< 30 days), CVI and mortality were analysed.

The exclusion criteria included: patients with restenosis of carotid arteries, stenosis of carotid arteries with associated stenosis of supraorbital branches, aneurysms of carotid arteries, carotid artery dissection, CEA and peripheral revascularisation performed in the same patient.

The CEA was performed with the eversion (E - CEA) and the classic (C - CEA) technique with Dacron patch, without the use of a shunt. Surgical treatment is indicated in asymptomatic patients with stenosis of 70 to 99 %, and in symptomatic patients with stenosis > 60 % (criteria for inclusion in the study). Stenosis is determined by Doppler ultrasound and CT angiography or MRI angiography. Basic data sources were computerised databases and standard histories of hospitalised patients (history, operating list, temperature list, letter of release). Anesthesiologists, vascular surgeons, participated in the evaluation of patients' clinical condition independently of each other.

Eversion carotid endarterectomy (E-CEA) technique implied carotid bifurcation level transection and removal of atherosclerotic plaque by artery eversion of ICA, then removal of plaque from an external carotid artery (ECA) and common carotid artery (CCA) and anatomic reimplantation of ACI. Classical carotid endarterectomy (C - CEA) technique was performed by longitudinal arteriotomy of CCA and ICA and by removal of atherosclerotic plaque. Arteriotomy was closed using a prosthetic patch. The later was used in cases of the small diameter of CCA and ICA (< 5 mm).

Statistical analyses

The statistical analyses were performed with SPSS (v. 21.0, SPSS Inc., Chicago, Illinois, USA). We compared clinical characteristics between group 1 and group 2 for qualitative variables using Mann - Whitney U test and Student's t-test. Chi-squared, using Yates correction and Fisher's exact probability test, was used to compare categorical variables. A probability value of < 0.05 was considered statistically significant.

Results

Of the 270 patients involved in the study, group 1 had 100 female patients and in the group 2 170 male pateints. The mean age in group 1 was 66.01 years (SD 8.42, ranging from 46 to 86 years), in group 2 66.46 years (SD 8.03, ranging from 47 to 85 years). Dacron patch (in C - CEA patients) was used in 41 subjects in group 1 (41%) and in 31 group 2 (18.2%). The risk factors (smoking, DM, HTA, HLP, CAD) indicates a higher number in group 2 but the observed difference is not statistically significant: smoking: 46 (46%) versus 73 (42.9%); p = 0.717, HTA: 92 (92%) versus 148 (87.1%); p = 0.295, HLP: 87 (87%) versus 141 (82.9%); p = 0.475, DM: 35 (35%) versus 55 (32.4%); p = 0.751 and CAD: 20 (20%) versus 44 (25.9%); p = 0.342, (Table 1).

Table 1: Patient's demographic data, risk factors, and comorbidities

	Group 1 (N = 100, 37%)	Group 2 (N = 170, 63%)	P-value
Mean age (yr)	66.01 ± 8.42	66.46 ± 8.03	0.659
Arterial hypertension	92 (92%)	148 (87.1%)	0.295
Diabetes mellitus	35 (35%)	55 (32.4%)	0.751
Hyperlipidemia	87 (87%)	141 (82.9%)	0.475
Smoker	46 (46%)	73 (42.9%)	0.717
Coronary artery disease	20 (20%)	44 (25.9%)	0.342

HTA - Arterial hypertension; DM - Diabetes mellitus; HLP - Hyperlipidemia; CAD - Coronary artery disease.

The incidence of symptomatic stenosis of carotid arteries was not statistically significant

between groups (group 1: (62 (62%) and in group 2: 103 (60.3%), p = 0.921). A statistically significant difference between symptoms of carotid stenosis in groups was observed only in patients with TIA (group 1: 19 (19%) versus group 2: 14 (8.2%), p = 0.016), vertigo (group 1: 23 (23%) versus group 2: 46 (27.1%), p = 0.682), small CVI (group 1: 11 (11%) versus group 2: 24 (4.1%), p = 0.582), amaurosis fugax (group 1: 9 (9%) versus group 2: 19 (11.2%), p = 0.719). There was no statistically significant difference in the number of asymptomatic patients between groups (group 1: 38 (38%) versus group 2: 67 (39.4%), p = 0.92), patients with bilateral stenosis (group 1: 32 (32%) versus group 2: 72 (42.4%), p =0.119) and contralateral occlusion (group 1: 11 (11%) versus group 2: 9 (5.3%), p = 0.137).

The average duration of surgery and clamping time was statistically significantly lower in group 2: duration of surgery (group 1: 103.45 min (SD 15.41) ranging from 75 min to 130 min versus group 2: 97.46 min (SD 13.87) ranging from 75 min to 130 min, p = 0.002), carotid artery clamping time (group 1: 19.58 (SD 5.43) in the range of 11 min to 32 min versus group 2: 17.61 (SD 4.82) in the range of 10 min to 35 min, p = 0.005). In women, the number of C - CEA in which patch was used was statistically significantly higher than in man (41 (41 %) versus 31 (18.2 %), p = 0.005), while the number of bilateral CEAs (formerly CEA contralateral) was not statistically significance between groups (group 1 10 (10%) versus group 2 21 (12.4%), p = 0.695), (Table 2).

Table 2: Clinical and anatomical features and surgical variable

	Group 1 (n = 100)	Group 2 (n = 170)	p – value
Preoperative symptoms	62 (62%)	103 (60.6%)	0.921
TIA	19 (19%)	14 (8.12 %)	0.016
Amaurosis fugax	9 (9%)	19 (11.2%)	0.719
CVI	11 (11%)	24 (14.1 %)	0.582
Vertigo	23 (23%)	46 (27.1%)	0.682
Asimptomatic patiens	38 (38%)	67 (39.4%)	0.92
Bilateral stenosis	32 (32%)	72 (42.4%)	0.119
Contralateral occlusio	11 (11%)	9 (5.3%)	0.137
Time of clamping ICA	19.58 ± 5.43	17.61 ± 4.82	0.005*
Operative time	103.45 ± 15.41	97.46 ± 13.87	0.002*
Patch closure	41 (41%)	31 (18.2%)	0.005*
Bilateral CEA	10 (10%)	21 (12.4%)	0.695

TIA - Transient ischemic attack; CVI - cerebrovascular insult; ICA - internal carotid artery.

Analysis of perioperative complications (< 30 days) CVI and/or mortality did not indicate a statistically significant difference between the analyzed groups 1 and 2 (stoke 7 (7%) versus 6 (3.5%), p = 0.242, death 2 (2%) versus 0.6% p = 0.557; stoke/death 9 (9%) versus 7 (4.1%); p = 0.169, all retrospectively). The total incidence of perioperative complications during the study was 16 (5.9%), (Table 3).

Table 3: Perioperative (< 30 days) complication

	Group 1 (n = 100)	Group 2 (n = 170)	p - value	Total (n = 270)
Stroke	7 (7%)	6 (3.5%)	0.242	13 (4.8%)
Death	2 (2.0%)	1 (0.6%)	0.557	3 (1.1%)
30 - day and Stroke/death	9 (9%)	7 (4.1%)	0.169	16 (5.9%)

Discussion

After the first CEA made by De Bakey [17], the same was established as a safe and effective method for lowering the risk of CVI in patients with significant stenosis of carotid arteries. Today, the CEA is a method with low mortality and incidence of perioperative complications, both in symptomatic [6] and in asymptomatic stenosis of carotid arteries [5] [7]. Two randomised studies of the 1990s have shown CEA's advantages over drug therapy for patients with moderate or severe internal carotid artery stenosis [7] [18]. The benefit of CEA in women remains, still, unclear.

The ACAS study showed a significant reduction of CVI risk in men versus women after CEA (66% versus 17%, retrospectively), most of these differences can be attributed to higher perioperative stroke and mortality rates in women compared to males (3.6 % versus 1.7 %, retrospectively) [7], other studies have reported similar results [4] [18] [19]. Recent large retrospective studies have been performed to assess the benefits and risks of CEA in women. Akbar et al. reported a series of 1298 CEA patients, of which 520 (40%) were women, with no differences in perioperative stroke between women and men (1.2% vs 1.7%, retrospectively). They concluded that female gender is not a risk factor for stroke, death or cardiac morbidity after CEA [15]. Also, Mattos et al. did not report an increased risk to a woman [14]. Similar results were found in our study where there was no statistically significant difference between female and male patients in perioperative complications (< 30 days) (9% versus 4.1%; p = 0.169, retrospectively). Unlike our research, there are newer researchers suggesting an increased risk for women [9]. Our research did not point a statistically significant difference in perioperative complications between men and women. Such results were obtained despite increased comorbidity (HTA, HLP, DM; smoking, CAD) in males, and despite smaller diameter of vessels and increased use of patch in women.

Like our study, Kapral et al. did not report a statistically significant difference in the presence of a contralateral occlusion in patients [20], and other studies did not report the correlation of contralateral occlusion and increased the perioperative risk of CVI and death [21] [22]. Statistically, significantly higher CEA using C - CEA (using prosthetic patch) technique is in women (41 (41%) versus 31 (18.2%), p = 0.005) is associated with a smaller blood vessel diameter (CCA, ICA). There is also a markedly longer time for carotid artery clamping in women than in man (19.58 ± 5.43 versus 17.61 ± 4.82, p = 0.005 retrospectively), and duration of surgery for women than man (103.45 ± 15.4 versus 97.46 ± 13.87, p = 0.002, retrospectively). More gracile blood vessels require the use of patch when

closing the arteriotomy (thereby reducing the possibility of restenosis), which in turn extends the time of clamping and thus the length of the operation. Study Doriga et al. [23] as our does not indicate a significant difference in the prevalence of symptomatic and asymptomatic stenosis of carotid arteries in women.

According to the results of this study, there is no statistically significant difference in perioperative complications (< 30 days) between women and men. Thos results have been confirmed by previous studies. The reason for this kind of results can be found in a relatively small sample of the patients, and in lager studies, there is a possibility for different results.

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Clinical Science

The Effect of Technological Devices on Cervical Lordosis

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Keywords: Cervical flexion; Cervical lordosis; Cervical pain; Mobile phone usage; Technological devices

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Abstract

PURPOSE: There is a need for cervical flexion and even cervical hyperflexion for the use of technological devices, especially mobile phones. We investigated the effect of this use on the cervical lordosis angle.

MATERIAL AND METHODS: A group of 156 patients who applied with only neck pain between 2013–2016 and had no additional problems were included. Patients are specifically questioned about mobile phone, tablet, and other devices usage. The value obtained by multiplying the year of usage and the average usage (hour) in daily life was determined as the total usage value (an average hour per day x year: hy). Cervical lordosis angles were statistically compared with the total time of use.

RESULTS: In the general ROC analysis, the cut-off value was found to be 20.5 hy. When the cut-off value is tested, the overall accuracy is very good with 72.4%. The true estimate of true risk and non-risk is quite high. The ROC analysis is statistically significant.

CONCLUSION: The use of computing devices, especially mobile telephones, and the increase in the flexion of the cervical spine indicate that cervical vertebral problems will increase even in younger people in future. Also, to using with attention at this point, ergonomic devices must also be developed.

Introduction

Over the years, the use of tablets, mobile phones and interactive computing devices has increased. Social and business life is now almost a part of our lives, and after this point, our life will be more affected. We do not know the damages that the mobile phones give to the spine, especially cervical region, which makes our work easier and is a part of our daily life. In the age of we live, our posture of cervical flexion is increased. Many people use their phones for hours during the day with the increasing use of social media, and this has been taking place in our lives for almost 15-20 years.

Also, the use of tablets and PC's is much higher. There is a need for flexion of the cervical region to use these devices, especially mobile phones. Increased cervical flexion has a negative effect on cervical lordosis.

We tried to investigate the relationship between the duration of use and cervical lordosis. This is the first study to show how technological devices affect spinal alignment regarding usage time.

Material and Methods

Patients with a complaint of neck pain in the young age population who applied to our polyclinic between 2013 and 2016 and did not have any additional problems were included in this study. The age range of patients in the study is 25-42. Patients are specifically questioned about mobile phone, tablet, and other devices (as gaming consoles) usage. They were asked how many years they have been using and how many hours in a day they spent in the flexion /hyperflexion posture. The value obtained by

multiplying the year of usage and the average usage (hour) in daily life was determined as the total usage value. Criteria that we applied when we included patients in the study;

1 - Desk workers and people working in the cervical flexure posture were excluded from the study.

2 - Patients with the condition that could affect the spine were excluded from study (rheumatic diseases, ankylosing spondylitis, deformities, connective tissue disease, previous spine surgery, and significant cervical trauma)

3 - Patients who read books regularly in flexion posture were excluded from the study.

Patients were not grouped because there was not a risky value for cervical lordosis accepted in the literature, and the cut-off was taken as median value firstly. And after general ROC analysis was performed and the sensitivity and specificity of the cut off value obtained here were compared. The cervical lordosis angles were measured by the tangent method in the position of lateral neutral standing (Figure 1). Cervical lordosis angles were statistically compared with total time (year x daily hour) of usage.

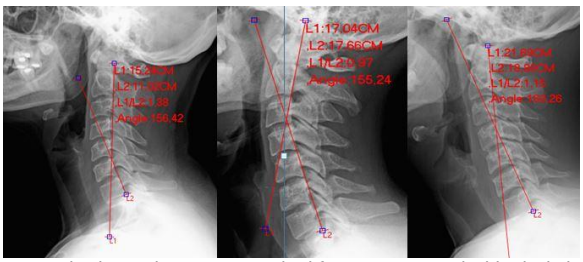

Figure 1: It is shown the tangent method for measure cervical lordosis in our some case

Results

The cut-off value for risk differentiation was set at 12.5 degrees because of the median value of 12.5 degrees for lordosis. According to this, patients with lordosis angle < 12.5 degrees were considered "risky" lordoz angle, patients with lordozis > 12.5 degrees were considered "non-risky" lordosis angle. In this case, 50 % of the patients are in the lordosis risk group, and 50 % are not in the lordosis risk group (Table 1).

Table 1: Descriptive Statistics

		Frequency	Percent
Gender	Female	93	59.6
	Male	63	40.4
Lordosis Risk Group	Non-Risky	78	50.0
	Risky	78	50.0
		Mean	SD
Lordosis Angle		13.24	12.21
Age		33.70	5.51
Usage Time		21.38	13.60

Lordosis Risk Group is divided by the median value of 12.5 degrees.

The average age of the patients was 33.7, the mean duration of use was calculated as 21.38 he and the mean lordosis was 13.24 degrees. 59.6% of the patients were female, and 40.4% were male (Table 1). In the general ROC analysis, the cut off value was found to be 20.5 hy. When the cut off value is tested, the overall accuracy is very good with 72.4%. The true estimate of true risk is 71.8 %, and the true estimate of the true non-risk estimate is 73.1% The ROC analysis is statistically significant (Table 2).

In the ROC analysis for women, the cut off value was found to be 17.5 hy. When cut off value is tested, total accuracy is good with 69.9 %. While the true estimate of true risk is 63.6 %, the true non-risk estimate is 78.9 % The ROC analysis for women is statistically significant (Table 2).

In the ROC analysis for men, the cut off value was found to be 20.5 hy. The best estimate compared to total and women was realised in men ROC analysis. When cut off value is tested, total accuracy is good with 76.2%. While the true estimate of true risk is 61.3%, the true non-risk estimate is 67.5%. The ROC analysis for men is statistically significant (Table 2).

Table 2: ROC Analysis Results

	Total Usage Time	Female Usage Time	Male Usage Time
Cut-Off*	20.5	17.5	20.5
Sensitivity	71.8%	63.6%	91.3%
Specificty	73,1%	78.9%	67.5%
PPV	49.4%	46.2%	54.0%
NPV	50.6%	53.8%	46.0%
AUC	0.779	0.794	0.819
Accuracy	72.4%	69.9%	76.2%

* Usage times are shown as hy (hour x year); PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under the curve.

The relationship between the lordosis risky group and gender has been examined. While 59.1% of the women were in the risky group, the rate of risky lordosis group in males was calculated as 36.5%. The difference was statistically significant (Table 3).

Table 3: The relationship between the Lordosis Risk Group and Gender was examined

Gender * Lordosis Risk Group Crosstabulation					
			Lordosis Risk Group NonRisky	Risky	p
Gender	Female	Count	38	55	< 0.005
		% within Gender	40.9%	59.1%	
		% within Lordosis Risk Group	48.7%	70.5%	
	Male	Count	40	23	
		% within Gender	63.5%	36.5%	
		% within Lordosis Risk Group	51.3%	29.5%	
Total		Count	78	78	
		% within Gender	50.0%	50.0%	
		% within Lordosis Risk Group	100.0%	100.0%	

*Fischer's Exact Test; Lordosis Risk Group is divided by the median value of 12.5 degrees.

The lordosis risk group and mean of usage were compared. The mean duration of total usage was 27.69 hy ± 12.67 hy in the group with lordosis < 12.5 as we said not a risky population, whereas it was calculated as 15.06 ± 11.44 hy in the group with lordosis > 12.5 as we said risky population. The difference was statistically significant ($p < 0.0001$) (Table 4).

Table 4: The relationship between the lordosis risk group and the average of usage time was compared

Lordosis Risk Group and Total Usage Time				
		Usage Time		p
		Mean	SD	
Lordosis Risk Group	Non-Risky	15.06	11.44	< 0.0001
	Risky	27.69	12.67	

Lordosis Risk Group is divided by the median value of 12.5 degrees.

Discussion

The cervical lordosis is the curve of the cervical vertebrae. Cervical lordosis provides horizontal gaze. Cervical lordosis helps to keep the spine in balance, provides it by turning to lordosis from kyphosis in the junction at the cervicothoracic region.

There is no clear study of the physiological curve in the cervical region. It has been stated that there may be differences in many people. The average accepted lordozis angle 20-35 [1] [2] [3] [4] [5]. However, there is no consensus on under which angle of the cervical lordosis can cause problems.

Many conditions affect cervical lordosis. Trauma, working postures in the job, and degenerative diseases affect cervical lordosis. Increased flexion/hyperflexion in the cervical region causes changes in the cervical region. Because of the prolonged tendency to flexion, the weight effect created by the weight of the head and the strain of the neck muscles will cause degeneration of the cervical vertebrae and discs, loss of lordosis and kyphosis. Cervical muscles are strained, ligamentous structures are deteriorating. These are the most important causes of loss of cervical lordosis. As a result of this, cervical disc degenerations, kyphotic cervical stenosis, cord tension, radicular symptoms are encountered [6] [7] [8].

Cervical colon separated to the 3 division by Luis. The anterior column is the disc and the vertebral body while the posteriors are defined as facet joints. The primary loading segments of the cervical column will be affected by the loss of cervical lordosis, which will accelerate the degeneration and the developing sagittal imbalance [9].

Deviations from this curvature, such as a loss of lordosis or the development of cervical kyphosis, are associated with pain and disability [2] [10] [11] [12] [14] [14].

There have been many publications on cervical lordosis and neck pain. While some studies found no correlation between cervical lordosis and neck pain, and some studies found strong correlations between neck pain and cervical lordosis [15][16][17][18][19].

In 1994, Helliwell stated that in patients with chronic neck pain, the cervical lordosis angle is more straight or less [20].

The normal lordotic angle has been shown to be different in many studies because the cervical spinal region is the most mobile segment of the spinal column [2] [12].

In the study of Mc Aviney et al. in 2005, cervical X-rays and angular measurements and examining neck pain, they noted that neck pain was statistically high in cervical curvature less than 20 degrees and could be considered clinically normal at above 30 degrees [13].

Mobile phones and technological devices have begun to be used more and more in our lives in the last 20-30 years. For using these devices, especially mobile phones, the cervical region's flexion and hyperflexion are essential. The flexion posture of the neck and the weight of head are disturbing the balance of the spine. Also, the use of technological devices and the duration of use during the day increases. The load on the cervical spine while using mobile phones in the cervical region has already been published before [6].

According to the degree of flexion, the stress in the cervical region increases, loads on discs increase, loss of lordosis and degenerative processes accelerate. This can be the source of pain. However, loss of lordosis will lead to greater pathological problems in the later period. It was pointed out in an issue in an article published in 2014. It has been tried to take attention to the danger waiting for us by giving numerical data. In the article, it was estimated that the average time spent in college with reading books and mobile devices in the flexion posture was 5000 hours [21].

The effect of mobile devices on our lives was studied, and the most common symptom was found to be neck pain even in young patients in the study of Azaria et al. [22]. They reported a problem as high as 72.1 %.And the increase in the intensity of use has also increased the symptom of neck pain, which is very short compared to the work we do [22].

The existence of neck symptoms in association with cell phone usage has been previously described, but it is very rare.The association between the degree of cervical lordosis and the usage time of mobile devices has never been mentioned before. We studied the effect of total time of usage on cervical lordosis in our study.

We considered the usage duration as a numerical value and assessed whether it correlated with the cervical lordosis regardless of pain score. Although we think that neck pain is related to cervical lordosis in general, we did not include the pain score in this study. Patients may be able to live pain periodically at different grades, so we made only an angular evaluation to be more objective.

We were meticulous when choosing patient populations. We worked on a young patient population. Our goal here is that this population is relatively remote from the expected degenerative processes with age, and the duration of usage is higher in this population.For this reason, we think the correlation will be more meaningful.

There are two different main methods of measuring cervical lordosis. Cobb and Harrison posterior tangent methods for cervical lordosis measurements have high reliability in evaluating cervical lordosis and are the most commonly used methods in practice [23] [24].

However, due to the degenerative changes in the cervical region, the use of the inferior vertebral endplates in the Cobb method showed that this method is lower in diagnostic accuracy than the tangent method, which uses the posterior edges of the vertebral corpus. So we chose Harrison posterior tangent method.

The relation of the Harrison posterior tangent method to the effective lordosis was found to be higher than the Cobb method, and also the measurement technique is more practical [24].

As a result of our study, cervical lordosis decreases in the correlation between total duration of usage. Especially the values of 20.5 hy were accepted as a critical threshold in patients.

So, according to the statistical analysis, approximately a value of 20 hy is lowered cervical lordosis under 12.5 degrees nearly 70 % in the population. An average of 2 hours per day during a 10-year period creates a risk of loss of cervical lordosis. There are some rehabilitation aimed at the loss of cervical lordosis, and it was written that they are useful. Anterior head weighting procedures were applied for loss of cervical lordosis in a study and improvement of cervical lordosis has been seen in patients [25].

We are all at risk in this age. Maybe we all need cervical rehabilitation. Or using such mobile devices without cervical flexion will relatively protect our cervical spine. Otherwise, cervical spine pathologies may be a problem that we will all encounter.

In conclusion, cervical vertebrae problems that will develop with the necessity of flexion of the cervical region and lifestyle in this way will also force our lives in the future. As a result of our study, cervical lordosis decreases in the correlation between total duration of usage. Especially the values of 20.5 hy were accepted as a critical threshold in patients. This situation is likely to lead to the loss of cervical lordosis in the following years and to cause serious problems associated with it.

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Clinical Science

Myasthenia Gravis and Associated Diseases

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Abstract

BACKGROUND: Myasthenia gravis (MG) is an autoimmune disease caused by the action of specific antibodies to the postsynaptic membrane of the neuromuscular junction, leading to impaired neuromuscular transmission. Patients with MG have an increased incidence of other autoimmune diseases.

AIM: to determine the presence of other associated diseases in patients with MG.

METHOD: A group of 127 patients with MG followed in 10 years period, in which the presence of other associated diseases has been analysed.

RESULTS: The sex ratio is in favour of the female sex, the average age of the initial manifestation of the disease is less than 50 years, 65.4% of the patients with MG have another disease. 15.0% patients have associated another autoimmune disease. Thyroid disease is the most common associated with MG, rarely rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and other autoimmune diseases. Other diseases include hypertension, heart disease, diabetes, respiratory diseases, dyslipidemia. 10.2% of the patients are diagnosed with extrathymic tumours of various origins.

CONCLUSION: Associated diseases are common in patients with MG, drawing attention to the possible common basis for their coexistence, as well as their impact on the intensity and treatment of the disease.

Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by a variety of complex mechanisms of action of specific antibodies to the postsynaptic membrane, leading to impairment of the function of the neuromuscular junction (NMJ) and neuromuscular transmission.

Cardinal clinical features are the weakness and fatigue of different, specific muscle groups with characteristic distribution, which increase with activity, and are improved with rest [1] [2].

The thymus plays a central role in the pathophysiology of MG due to the presence of the key elements of the myasthenic autoimmune process, such as antigen presenting cells, T and B cells. Approximately 80% of patients with MG have thymic abnormalities; up to 70% of patients have thymic hyperplasia, 10 - 15% of thymomas, and in 15 – 20% thymus is normal or regressive, i.e. atrophic and replaced with fat tissue [3] [4] [5].

Current trends in the treatment of MG arise from the pathogenesis of the disease and provide satisfactory control in most patients. However, the course of the disease and the outcome of the treatment may be affected by other conditions:

associated autoimmune diseases (AD), diseases common in the general population or tumours [2] [4].

In some patients, these diseases occur before, and in others after the manifestation of MG.

This study is aimed to assess the frequency and type of comorbidity in the examined group of patients with MG.

Methods

An observational study of 127 patients with MG monitored retrospectively and prospectively on the Neurology Clinic in 10 years period. The demographic characteristics of patients, the clinical manifestation of the disease, thymectomy, thymic pathology and the presence of associated diseases have been analysed.

The diagnosis of MG was confirmed by clinical examination, by the positive response to Prostigmin, specific antibody testing, neuromuscular weakness response to repetitive nerve stimulation test, computed tomography (CT) on the anterior mediastinum.

The severity of the disease was defined according to the classification of Osserman-Jankins, modified by Abt PL et al. (2001) [6] [7].

Patients with MG were monitored with regular neurological examinations, and other investigations were performed depending on the clinical manifestation of the associated conditions.

The diagnosis of thyroid disease is based on clinical features, examination, laboratory findings and ultrasound examination.

The diagnosis of Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) is set according to the Criteria of the American College of Rheumatology (ACR) [8] [9].

Statistics: Statistical analysis is made in statistical programs: STATISTICA 7.1; SPSS 17.0 (Difference test, Pearson Chi-square).

Results

All 127 patients included in the study have a confirmed diagnosis of MG. The basic demographic and clinical characteristics of patients are shown in Table 1; average age in MG patients with or without associated autoimmune disease is shown in Table 2, and Table 3 presents the characteristics of patients with MG and associated disease.

Table 1: Characteristics of the total number of patients with MG in the study

Gender	*N*	*%*
Female	81	63.8
Male	46	36.2
Age (years)	*N*	
≥ 50	70	55.1
< 50	57	44.9
Age at diagnosis (years)	*Average*	*N*
Female	44.5	81
Male	56.5	46
n=127	48.8	127
Age at onset (years)	*Average*	*N*
Female	43.3	81
Male	55.7	46
N=127	47.8	127
Comorbidity	*N*	*%*
Yes	83	65.4
No	44	44.6
Associated autoimmune disease	*N*	*%*
No	108	85
Yes	19	15
Hypothyroidism		*%*
Yes	12	9.4
Hyperthyroidism		
Yes	4	3.1
Sle		
Yes	1	0.8
Ra		
Yes	2	1,6
Vasculitis		
Yes	1	0.8
Thrombocytopenia		
Yes	1	0.8
Heart disease		
Yes	31	24.4
Hypertension		
Yes	60	47,2
Diabetes mellitus		
Yes	18	14,2
Dyslipidaemia		
Yes	14	11
Respiratory disease		
Yes	17	13.4
Tumors		
Yes	13	10.2

*SLE -systemic lupus erythematosus; *RA-rheumatoid arthritis.

The sex ratio is 1.9: 1 in favour of the female sex, statistically significant, p = 0.0001.

The difference in the average age at the first symptoms, which is higher in men, is statistically significant, p = 0.001564 (Table 1).

MG with late onset (over 50 years) have 55.1%, and with early onset (under 50) have 44.9% of the patients, statistically non-significant, p = 0.1040 (Table 1).

Majority of 83 (65.4%) patients with MG have another disease, p = 0.0009 (Table 1).

Older than 50 years are 81.9%, younger than 50 years, are 18.1 % of patients with comorbidity, p = 0.0001, (Table 2 and 3).

Table 2: Mean age in patients with MG with/without associated autoimmune disease

Without	With	t-value	Df	P	Without	With	Sd-without	Sd- with
47.25	51.0	-0.712645	125	0.477394	108	19	21.55329	18.58614

A subgroup of 73 from a total of 83 (88%) patients with comorbidity present a generalised form of the disease, while 10 (12%) have an ocular form of the disease.

Table 3: Characteristics of patients with MG with associated disease

Gender	*N=83*	*%*
Female	51	61.4
Male	32	38.6
Age (years)	*N*	
≥ 50	68	81.9
< 50	15	18.1
Age at diagnosis (years)	*Average*	*N*
Female	55.8	51
Male	67.6	32
Age at onset (years)	*Average*	*N*
Female	54.8	51
Male	66.7	32
Associated autoimmune disease	*N=19*	*%*
≥ 50	11	57.9
< 50	8	42.1
Hypothyroidism	*N=12*	
≥ 50	7	58.3
< 50	5	41.7
Hyperthyroidism	*n=4*	
≥ 50	2	50
< 50	2	50
Sle		
≥ 50	1	100
Ra		
≥ 50	2	100
Vasculitis		
≥ 50	1	100
Thrombocytopenia		
≥ 50	1	100
Heart disease	*N=31*	*24,4%*
≥ 50	30	96.8
< 50	1	3.2
Hypertension	*N=60*	*47,2%*
≥ 50	57	95
< 50	3	5
Diabetes mellitus	*N=18*	*14,2%*
≥ 50	17	94.4
< 50	1	5.6
Dyslipidaemia	*N=14*	*11%*
≥ 50	11	78.6
< 50	3	21.4
Respiratory disease	*n=17*	*13,4%*
≥ 50	17	100
Tumors	*N=13*	*10,2%*
≥ 50	11	84.6
< 50	2	4

*SLE -systemic lupus erythematosus; *RA-rheumatoid arthritis.

Associated autoimmune diseases (AD)

Nineteen (15.0%) patients have associated another AD, 11 (57.9%) are older than 50 years. (≥ 50 years), and 8 (42.1%) are younger than 50 years. (< 50 yrs) (Table 3). In 14 (73.7 %) of them, the associated AD was diagnosed before MG. Fifteen 15 (78.94 %) are women; 8 (53.3%) are younger, and 7 (46.7%) are older than 50 years. Men are 4 (21.06%), and all have late-onset MG (≥ 50 years). Sixteen (12.6 %) have thyroid disease (Table 3).

The generalised form of MG have 14 patients (87.5%) (11 with hypo-, 3 with hyperthyroidism), and with ocular form, there are 2 patients (one with hypo and hyperthyroidism). Two (1.6%) of the patients have rheumatoid arthritis (RA) and a generalised form of MG (Table 1). One patient (0.8%) is with SLE, with a generalised form of MG. One patient (0.8%) is with vasculitis and a generalised form of MG, and one (0.8%) with thrombocytopenia and ocular MG (Table 1).

Patients with vasculitis and thrombocytopenia are considered separately from other patients with the confirmed associated AD. In these patients, the aetiology of the condition has not been confirmed with certainty, but according to immunological tests, the probability of their immunological basis is high.

One patient has MG and two associated AD - RA and hypothyroidism. From the 19 patients with the associated AD, 15 (78.9%) were generalised, and 4 (21.1%) had an ocular disease. There is no significant association between the clinical form of MG and the associated AD (Table 4).

Table 4: Association between the clinical form of MG and the associated AD

Associated autoimmune disease	Pearson Chi-square	p
Hypothyroidism	0.546045	0.45994
Hyperthyroidism	0.291224	0.58944
SLE	0.185305	0.66685
RA	0.375129	0.54022
Vasculitis	0.185305	0.66685
Thrombocytopenia	5.52734	0.01872

In patients with MG and associated AD, AChR antibody tests were done on 6: the results were positive on 4 patients, from which 2 were non - thymectomized with Graves's disease and 2 thymectomized patients were with hypothyroidism (Hashimoto thyroiditis), with micro microthymoma B1B2, thymic hyperplasia. The other 2 patients with rheumatoid arthritis and hyperthyroidism (Graves's disease) were negative for the antiAChRat.

Other associated diseases

All patients have a generalised form of the disease, and most are older than 50 years (Table 1 and 3). There is no significant association between severity of MG and associated disease (Table 5).

Table 5: Association between severity of MG and other diseases

Another disease	Pearson chi-square	P
Hypertension	0.036403	0.84869
Diabetes mellitus	0.797006	0.37199
Heart disease	5.63665	0.01759
Dyslipidaemia	0.455038	0.49995
Respiratory disease	1.49967	0.22072

Tumors

Thirteen (10.2%) patients were diagnosed with extrathymic tumours of different origin (Table 1), 11 (84.6%) were with late-onset MG (Table 3 and 6).

Table 6: MG patients with extrathymic tumours

MG/tumor N=13	
Before MG dg	*After MG dg*
Prostate cancer 1	Malignant melanoma 2
Breast cancer 1	Adrenal tumour 1
Kidney cancer 1	
Basocellular skin cancer 1	
Uterine tumour 2	
Tonsil tumour 1	
Parotid gl. tumour 1	
Breast fibroid tumour 1	
Brain meningioma	

Some patients with extrathymic tumours, also have associated autoimmune disease other than MG - rheumatoid arthritis, hypothyroidism, vasculitis.

Thymectomy

A group of 23, from a total of 83 patients (27.7%), are thymectomized (Table 7).

Table 7. Thymus histology

Thymus histology	N = 23
Thymic hyperplasia	15 (65.2%)
Thymoma (3 malignant t, thymoma AB 1, thymoma B1B2 1)	5 (2.7%)
Thymic atrophy/fatty replacement	2 (8.7%)
Persistent thymus	1 (4.3%)

From the 19 patients with the associated autoimmune disease, 7 (36.8%) underwent thymectomy; 5 (71.4%) had thymic hyperplasia, all women, with an average age of 32.8 years. (min 20, max 56), and only one had positive antiAChRat.

In these 5 patients with thymic hyperplasia and associated autoimmune disease, 4 were with hypothyroidism, and one patient with SLE.

Two of the operated patients with hypothyroidism (Hashimoto thyroiditis) had thymoma, and late-onset MG, average age - 64 years, one patient had + antiAChRat, and the other was not tested.

Other patients with thymus pathology had hypertension, heart and respiratory diseases, diabetes, dyslipidemia.

Discussion

Autoimmune diseases are a heterogeneous group of diseases caused by loss of immune tolerance to their antigens in which multiple alterations to the immune system result in a spectrum of syndromes that either target specific organs or the whole body [10].

The incidence is approximately 80/100,000 inhabitants per year, approximately 5% of the population is affected by one or more autoimmune diseases, and the prevalence is higher in women than men. In patients with one AD, there is a greater risk of developing another AD, or more. The common influence of the genetic, immunological, hormonal and environmental factors is considered to be the cause of these diseases [5] [10] [11] [12] [15].

Patients with MG have an increased incidence of other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto thyroiditis, Graves' disease and pernicious anemia, and the frequency varies widely: from 8.7 to 25%, 13 to 22%, while the rates of association in the Norwegian and Danish studies are 22.9%, i.e., 9.4% [13][14][15][16].

In MG with the associated AD, the female patients, with early - onset and generalised MG are predominant, although the other group, late-onset MG, exhibits an increased risk of associated AD compared with the general population [17].

Associated AD varies among different MG subgroups. Thymus hyperplasia is considered to be at greater risk for the associated AD, unlike MG with other than antiAChR types of antibodies (to titin, or to a ryanodine receptor) are associated with a lower risk [17].

Thyroid disease is the most common AD associated with MG, with a prevalence of 5 – 10%, while MG is present in 0.2% of the patients with diagnosed autoimmune thyroid disease [14].

Acute disease and the use of corticosteroids affect the thyroid function, but at the same time, corticosteroids have a positive effect due to their immune - regulatory function associated with the proliferation of AChR (acetylcholine receptors) [18] [19].

In various studies, these diseases are differently represented, but the most common is the hypothyroidism (Hashimoto thyroiditis) about hyperthyroidism (Graves' disease) [20] [21]. MG - associated autoimmune thyroid disease is considered to have a milder form, and the ocular form has a special relationship with it [22]. The explanations for this association are: a) ocular and generalised MG are considered as two different diseases that may be associated with various other autoimmune conditions; b) cross - immune response to epitopes or autoantigens common to thyroid and eye muscles; c) genetic basis [23] [24].

The prevalence rate of coexistence of SLE and MG in published studies is usually around 2.6%, but in the study of Sthoeger Z. et al. on 78 patients, the rate rises to 7.7%, with greater prevalence of women [25] [26] [27].

MG is organ - specific (antibodies to AChR), while SLE is a systemic autoimmune disease affecting multiple organs, producing a wide spectrum of antibodies (targeted mainly to nuclear antigens and ds - DNA) and impaired T and B cell function [28].

Autoantibodies are the basis of immunopathogenesis for both diseases, and molecular mimicry, as a potential mechanism for initiating and/or maintaining the production of autoantibodies, is related to the association of MG and SLE. Also, there is a similarity among the segment of AChR for U1, the nuclear ribonucleoprotein that is an autoantigen marker for SLE, and a mixed connective tissue disease. Most of the antibodies in MG are targeted to a small region of the alpha subunit of the AChR, called the major immunogenic region. Various autoimmune diseases begin with a wide range of reactivity towards multiple autoantigens, and in MG, according to such structural similarities, the response to the main immune region of the acetylcholine receptor is polyreactive [28] [29].

Almost equal is the number of patients where MG is initially diagnosed, and thymectomy has been performed, and the same number of patients in whom SLE occurs after thymectomy, which imposes the dilemma about the role of thymectomy [30] [31].

Rheumatoid arthritis occurs in 4–7% of patients with MG, and after thyroid autoimmune disease, RA is frequently present [13] [14] [17] [18] [25]. Patients with MG as a result of RA treated with d-penicillamine [33] have also been described. None of our patients has been treated with d - penicillamine. Similarly, with the findings of the patients with SLE, RA manifestations are also less pronounced than those of MG.

It has been observed that the frequency of heart disease or increased mortality due to heart disease in patients with MG is equal to the prevalence of the general population [34].

The most common are cardiac rhythm disorders, sympathetic destabilisation, and especially parasympathetic function [35]. Particular attention deserves patients with MG and severe cardiomyositis, where the heart muscle can be the target of autoimmune inflammation in MG (antibodies to titin, striated muscles, ryanodine receptors which are detected in thymoma and elderly patients react with the heart muscle) [36] [37].

DM prevalence among MG patients varies from 2 – 3 % to 20 % in different studies [18].

In these patients, late MG is more frequent, unlike those without DM. It is more frequent in men than women (29 vs 16 %). Patients with MG and DM may have positive more organ-specific antibodies (with DM type 1), or onset of DM during corticosteroid therapy (DM type 2) [38]. Doses of prednisolone higher than 30 mg/day increase the level of glycaemia in patients who already have DM, and can cause glucose intolerance or diabetes in previously normoglycaemic subjects [39]. Therefore, it is unclear when corticosteroid therapy directly induces DM, or only accelerates the manifestation of the disease.

In most of the patients with MG, respiratory symptoms are manifested in the advanced stage of the disease, but in some patients, depending on the intensity of the weakness and fatigue, it can be acutely manifested. Chronic respiratory diseases and infections are the most common precipitating factor for severe respiratory muscle weakness [40] [41]. Thirty nine percentage (39%) of the patients have reduced vital capacity, and 19 % with severe generalised MG have experienced a myasthenic crisis with the need for assisted ventilation [34] [40].

A higher prevalence of dyslipidemia in MG was found in the general population - 60 vs 27%, even in patients who do not receive steroids (50%). It is more common in men, with late-onset MG. Treatment with statins preparations may cause exacerbations of MG [18] [42].

Hypertensive disease in patients with MG is less than half (15 vs 30%) in the general population, more commonly in men with late-onset MG, and with higher administered doses of corticosteroids [18].

The increased frequency of neoplasms in MG and other autoimmune diseases has long been detected. In older studies, the risk for neoplasms in MG is three times higher than expected and with a higher frequency of occurrence in the first year after diagnosis and before thymectomy. After surgery, the risk is reduced and is similar to that of the general population [43].

According to recent reports, the risk of an extrathymic tumour is higher in MG with thymoma [44] [45] [46], and reported prevalence rate is between 3 and 12% [46] [47] [48].

The nature and origin of tumours are different. According to some reports, solid tumours are most common, according to others, autoimmune diseases treated with immunosuppressive therapy are associated more often with the tumour of hematopoietic organs and skin [17] [47] [50].

The increased risk is explained by 1. the role of immune mechanisms in MG in the appearance of extrathymic tumours, especially after the diagnosis of MG, as a result of impaired immune response and immunosuppressive therapy; 2. common genetic predisposition to thymomas and other tumours; 3. exogenous factors [50].

According to the results of our analysis, majority of the malignancies have been diagnosed before MG and patients were not treated with immunosuppressive therapy for MG, the histological type, the late onset of the disease, disagree with those in studies in which the onset of malignancy is more common after the diagnosis of MG [49].

Patients with late-onset MG have an increased risk of malignant disease; have a more severe form of MG, probably due to the weakness and dysregulation of the immune system [47].

The role of thymectomy as a therapeutic modality in MG in the onset of associated autoimmune disease has not yet been fully clarified.

The thymectomy alone does not seem to affect the development of associated AD, but it can cause a decrease in tolerance to its antigens and be a risk factor for its occurrence through the lack of thymic hormones that cause disruption of the function of suppressor cells, and their substitution can lead to a partial return to their function. Experimental studies of the SLE model do not show either clinical or changes in antibody concentrations, so that thymectomy may not be the precipitating factor for the development of associated AD [17] [28] [29] [30] [32]. Studies in which the occurrence of the associated AD is before MG and thymectomy, explain it with the pathogenic effect of myasthenic thymus [31].

Only in one patient in this study, the associated AD occurs after the thymectomy, which supports the consideration of genetic predisposition to autoimmune diseases.

In conclusion, the significance of this study is that this research has been done for the first time in Macedonia. By using our materials, we have researched the occurrence and prevalence of other diseases in patients with MG. The results are mainly in line with the overall prevalence of all associated autoimmune diseases, and the most common autoimmune diseases of the thyroid gland are 12.6 %, but the rates of SLE, RA, thrombocytopenia, vasculitis are lower.

From the other associated diseases, the most frequent one is hypertensive disease; diabetes is in line with the published rates, and the least represented are dyslipidemia and respiratory diseases. The frequency of tumours of extrathymic origin is equal to the referenced publications but before the diagnosis of MG. The origins, character and severity of the conditions, which can occur with MG (before or after), impose the need to consider their influence on the clinical manifestation and treatment of the disease.

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Correlation of Procalcitonin and C-Reactive Protein with Intra-Abdominal Hypertension in Intra-Abdominal Infections: Their Predictive Role in the Progress of the Disease

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Abstract

AIM: To analyse the correlation of procalcitonin (PCT) and C-reactive protein (CRP) values with increased intra-abdominal pressure and to evaluate their predictive role in the progression of Intra-abdominal infections.

MATERIALS AND METHODS: A non-randomized prospective study conducted in the group of 80 patients. We have measured the PCT, CRP and intra-abdominal pressure (IAP).

RESULTS: According to IAH grades (G), there was a significant difference of PCT values: G I 3.6 ± 5.1 ng/ml, G II 10.9 ± 22.6 ng/ml, G III 15.2 ± 30.2 ng/ml ($p = 0.045$) until CRP values were increased in all IAH groups but without distinction between the groups: GI 183 ± 64.5, GII 196 ± 90.2, GIII 224 ± 96.3 ($p = 0.17$). According to the severity of the infection, we yielded increased values of PCT, IAP and CRP in septic shock, severe sepsis and SIRS/sepsis resulting in significant differences of PCT and IAP.

CONCLUSION: Based on the results of our research, we conclude that the correlation of PCT values with IAH grades is quite significant while the CRP results remain high in IAH but without significant difference between the different grades of IAH.

Introduction

Intraabdominal infections are defined as peritoneal inflammation in response to microorganisms [1]. Despite the achievements in the diagnosis, management, and proper treatment of patients with intra-abdominal infections the presence of secondary peritonitis reflects the critical prognosis, which has a high mortality rate of up to 30% [2] [3] [4] [5] [6]. Early prognosis estimation of complicatediIntra-abdominal infections is important in evaluating the severity of the disease sinceiIntra-abdominal infections might advance to severe sepsis and septic shock [4]. It is often associated with hypoperfusion followed by tissue damage and organ dysfunction following increased severity of systemic response to infection [7] [8] [9]. There are some promising biomarkers for sepsis that are currently used for relatively few diagnostic purposes [10]. Studies are aimed to find a single marker at low cost, that can be measured quickly, to repeat measurement easy, and that measurement does not cause disturbances in patients [11]. From this group of biomarkers, CRP and PCT are most commonly used in clinical practice [10]. CRP is the acute phase protein synthesised in the liver and is released after inflammation and tissue damage [12] [13].

In many studies, the role of PCT in the diagnosis and treatment of systemic and local infections was investigated, includingiIntra-abdominal infections [14]. PCT in secondary peritonitis has improved diagnostic value for identification of patients with severe sepsis endangered by septic shock [15]. Bacterial infection is a strong PCT stimulus, while viral systemic inflammation results in PCT values to be low [14][16]. In recent years, there was expressed interest iniIntra-abdominal hypertension (IAH) that is defined as a pathological increase ofiIntra-abdominal pressure above 12 mmHg [17]. IAH is determined by the elasticity of the abdominal wall/diaphragm, the volume

of internal organs and the presence of ascites, blood, and intestinal contents. Some abdominal clinical conditions (peritonitis, ileus, volvulus, pancreatitis, complications after abdominal surgery) and systemic conditions (sepsis, mechanical ventilation, pneumonia, and burns) found to be related with IAH [17].

The purpose of this prospective study is to compare the values of PCT and CRP with IAP grades toiIntra-abdominal infections and determination of the correlation between them, and correlation of these parameters about the severity of the infection, which points to their predictive role in evaluating the prognosis of the disease.

Materials and Methods

This is a prospective, controlled clinical trial involving hospitalised patients at the University Clinical Center of Kosovo in Pristina, registered in the period from July 2016 to February 2017. The research was conducted at the University Clinical Center of Kosovo, Pristina, where 80 patients were hospitalised as abdominal cases in whichiIntra-abdominal hypertension was present. The research protocol has been approved by the Ethics Committee within the University of Prishtina – Faculty of Medicine and the consent form is completed by all participants or their family members.

Inclusion Criteria: Age over 18 years, the presence of SIRS due toiIntra-abdominal infections, the presence of intra-abdominal hypertension, consent from the patient's relatives.

Exclusion criteria: Urinary trauma, urinary bladder injury, immunosuppression, chronic kidney failure, liver cirrhosis, SIRS is not present, long-term use of corticoids, acute hepatic insufficiency, diabetes.

Protocol and Treatment

The baseline criterion during the research was the measurement of the IAP before the operation every four hours, and it was evaluated as IAH if the average of these measurements was > 12 mmHg. The measurement was performed even after the operation, where the measurement was performed three times in 24h, and the mean was calculated for each day. The duration of the measurement has continued until the normalisation of the IAP. TheiIntra-abdominal pressure measurement was done by the method evaluated by Kron. PCT and CRP measurement were performed before surgery, after the 1st, 4th and 7th days and the following days after the surgery if necessary. The PCT marker level measurement is done with the Elecsys BRAHMS method. Laboratory measurements and analyses that are relevant to the designation of IAH / ACS (Intra - abdominal Hypertension / Abdominal Compartment Syndrome), MODS (Multiple Organ Dysfunction Score), APACHE II (Acute Physiology and Chronic Health Evaluation), SOFA (Sequential Organ Failure Assessment), IMP (Index Mannheim Peritonitis), MAP (Mean Arterial Pressure) were realized. The fluid balance in the body is determined based on the weight, ordinated juices, and diuresis APP (APP = MAP - IAP) before and after surgery, FG (FG = MAP - 2IAP) before and after surgery. Based on the clinical, laboratory and general findings, the severity ofiIntra-abdominal infection has been classified into three groups: SIRS/sepsis, severe sepsis and septic shock. At the same time, based on the values of IAP, patients are grouped into three groups: Grade I: IAP 12 - 15 mmHg, Grade II: IAP 16 - 20 mmHg, Grade III: IAP 21 - 25 mmHg. There are also cases involving ACS in GIII. In the realised measurements, we did not have cases with IAP > 25 mm Hg. The PCT and CRP relationships with IAP grades, APP, FG, diuresis and fluid balance also were analysed in correlation with these parameters according to the severity of the infection.

Statistical Analysis

Statistical data processing was performed with the statistical package SPSS 22.0. The arithmetic average, the standard deviation, the minimum and the maximum values were calculated. Spearman correlation coefficient was used for non - parametric data. Qualitative data testing was done with the Pearson's chi-squared test ($\chi 2$) and the exact Fisher test of quantitative data that had a normal distribution with T-test and One Way ANOVA, while those with non - normal distribution with the Mann - Whitney test or Kruskal Wallis test. The difference is significant if $P < 0.05$.

Results

In the study, procalcitonin and CRP were analysed about IAH of diagnoses of different structures withiIntra-abdominal infections.

In Table 1, we presented the patient's related characteristics and the diagnosis structure of these patients about the three grades of IAH. In the total cohort of patients, male patients were dominant in comparison to females (54 vs 26). The average age of the participants was 49.4 years (SD ± 18.3 years), ranging from 18 to 56 years. The results showed a significant difference ($P < 0.003$) between the age of the patients, the gender and the degree of IAH. First-degree hypertension was registered in 46 or 57.5%,

second degree in 24 or 30.0% and third degree in 10 or 12.5% patients. Regarding the diagnosis structure, acute perforated appendicitis with diffuse peritoneal diffuse has dominated all degrees of IAH In cases with SIRS/sepsis, the presence of GI hypertension was more common in severe sepsis, and septic shock GII and GIII of IAH were more pronounced. Abdominal Compartment Syndrome was present at 4 (5%) cases (Table 1).

Table 1: Characteristics of the patients involved in the study

	Intra-abdominal Hypertension			
	G I	G II	G III	P
Age	43.3 ± 17.5	57.3 ± 17.5	58.2 ± 14.2	0.003[a]
Female	15 (57.7%)	6 (23.1%)	5 (19.2%)	0.366[b]
Male	31 (57.4%)	18 (33.3%)	5 (9.3%)	0.366[b]
Appendicitis acuta gangrenosa perforativa. Peritonitis diffusa fibro purulenta	21	6	4	
Cholecystitis gangrenosa	2	2	-	
Dehiscencio suttura duodeni ,peritonitis diffusa fibropurulenta	1	-	-	
Duodenopancreatectomia cefalica,dehiscencio anastomosis pancreato-jejunalis	-	-	1	
Hernia ventralis per magna.Incarceratio intestine ilei et perforation ilei	-	-	1	
Dehiscencio entero - entero anastomosis	4	5	2	
Perforatio diverticulum Meckeli,Peritonitis seropurulenta	-	1	-	
Perforatio in loci GEA.Peritonitis diffusa	1	-	-	
Perforation liberal	4	2	-	
Perforatio sigmae,Colitis ulcerosa,peritonitis diffusa stercoralis	1	-	-	
St post histerectomiam.Peritonitis fibropurulenta	-	1	-	
Tu perforans colonies colonies	-	1	1	
Ulcus bulbi duodeni perforans. Peritonitis fibropurulenta	10	3	1	
Ulcus ventriculi perforans abscessus multiplices intestini	-	1	-	
Vulnus sclopetarium abdominis.Laesio intestine .peritonitis difusa	2	2	-	
SIRS/Sepsis	41 (70.69%)	14 (24.14%)	3 (5.17%)-ACS(n=1)	
Severe Sepsis	4 (25%)	6 (37.5%)	6 (37.5%)-ACS(n=2)	
Septic Shock	1 (16.7%)	4 (66.6%)	1 (16.7%)-ACS(n=1)	

a - Kruskal Wallis test, b- X^2 – test.

The PCT and mortality rates determined by the scales: APACHE, SOFA, IMP, MODS before surgery, which have been observed in higher results for IAH patients. All these parameters were statistically significant by IAH grades. CRP results to be increased at all levels of IAH but without statistical significance among groups. MODS was 0 % in 19 patients out of which 3 were with GII and 16 were with GI of IAH, at the same time, PCT in these cases was < 2 ng / ml except for only one case with PCT values of 10 ng/ml. SOFA mortality was < 10 % in 18 patients, 14 with GI and 4 with GII of IAH, and PCT > 2 ng/ml in one patient. The GII, GIII / ACS, values of FG, APP, diuresis and fluid balance were significantly reduced, and we have distinguished significant statistical significance of these parameters by IAH grades (Table 2).

Table 2: Predictive parameters in admission in accordance with intra - abdominal pressure degrees

	Abdominal Urgencies n = 80			
	GI (n = 46)	GII (n = 24)	GIII (n = 6)/CSA (n = 4)	P
PCT	3.6 ± 5.1	10.9 ± 22.6	15.2 ± 30.2	0.045[a]
CRP	183.7 ± 64.5	196.3 ± 90.2	224.4 ± 96.3	0.17[a]
FG	56.0 ± 10.8	48.7 ± 25	37.1 ± 16.2	0.005[b]
APP	69.1 ± 10.8	66.1 ± 24.2	56.3 ± 17.3	0.096[b]
Diuretics and fluid balance	1.0 ± 0.5	0.6 ± 0.4	0.4 ± 0.5	<0.0001[a]
SOFA-mortality	11.1 ± 14.2	28.8 ± 27.0	39.6 ± 24.9	0.0001[a]
APACHE II- mortality	12.3 ± 14.7	31.8 ± 26.9	40.4 ± 22.8	<0.0001[a]
IMP- mortality	15.0 ± 12.7	29.3 ± 24.2	38.6 ± 22.4	0.003[a]
MODS- mortality	7.3 ± 12.3	19.3 ± 22.5	26.2 ± 29.8	0.0004[a]

A - Kruskal Wallis test; b - One Way ANOVA. PCT - procalcitonin, CRP - C reactive protein, FG - Filtration gradient, APP - abdominal perfusion pressure, SOFA - Sequential Organ Failure Assessment, APACHE - Acute Physiology and Chronic Health Evaluation IMP - Index Mannheim peritonitis, MODS - Multiple Organ Dysfunction Score.

The analysis of the values of IAP and PCT in all cases involved in the research results with a significant positive correlation of a medium scale (r = 0.42, P < 0.0001) (Fig. 1).

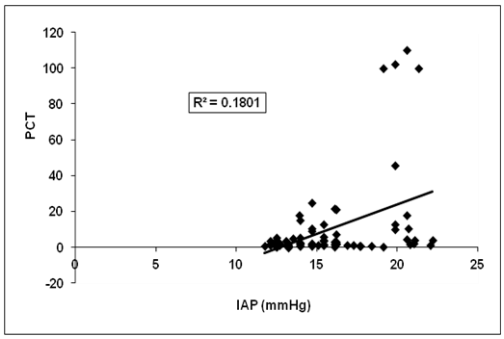

Figure 1: Correlation between intra-abdominal pressure and PCT values

A significant positive correlation of a middle degree was observed with the correlation of Sperman (r = 0.44, P < 0.0001) between IAP and CRP values (Fig. 2).

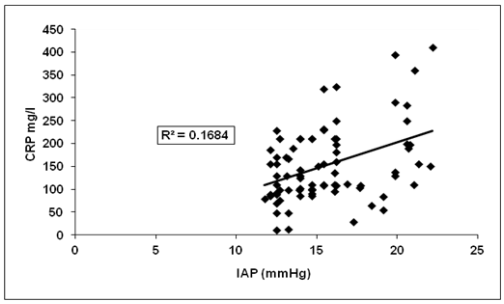

Figure 2: Correlation between intra-abdominal pressure and CRP values

Intra-abdominal pressures, analysed according to the severity of the infection, resulting in higher values for all groups. However, the statistical difference lies within the category of the infection before surgery and the following 4 - day post-surgery period. Even in PCT, we gained statistical significance by infection category before surgery, in day 1 and 4 post - surgery. CRP values were increased in all groups, but there was no significant difference according to the severity of the infection (Table 3).

Table 3: Correlation of PCT and CRP with IAH according to the severity of the infection

	Abdominal IUrgencies			
	Septic Shock	Severe Sepsis	SIRS/sepsis	P
IAP before Surgery	18.4 ± 2.8	18.3 ± 3.2	14.7 ± 2.3	0.0002[a]
IAP after surgery – day 1	16.4 ± 4.0	16.4 ± 3.2	11.8 ± 2.1	<0.0001[b]
IAP after surgery – day 2	16.5 ± 4.1	14.76 ± 3.6	10.1 ± 2.3	<0.0001[a]
IAP after surgery – day 3	15.8 ± 0.97	12.2 ± 3.71	9.8 ± 2.06	0.0031[a]
IAP after surgery – day 4	17.62 ± 8.37	11.31 ± 6.25	9.45 ± 0.72	0.0500[a]
PCT before surgery	49.2 ± 46.6	9.3 ± 12.1	3.1 ± 4.6	0.0002[a]
PCT after surgery – day 1	42.4 ± 48.2	6.5 ± 7.6	2.1 ± 2.6	0.0024[a]
PCT after surgery – day 4	43.3 ± 37.3	3.3 ± 3.4	0.8 ± 0.8	<0.0001[a]
CRP before surgery	189.9 ± 114.4	187.0 ± 90.2	140.6 ± 73.5	0.1447[a]
CRP after surgery – day 1	210.3 ± 117.1	124.7 ± 80.2	115.1 ± 64.7	0.894[a]
CRP after surgery – day 4	124.2 ± 98.2	101.2 ± 48.1	97.1 ± 51.8	0.264 [a]

a - Kruskal Wallis test; One Way ANOVA test.

Discussion

In this clinical study, PCT and CRP correlation with IAH and their predictive role in evaluatingiIntra-abdominal infections with peritonitis were evaluated. Our findings indicate a significant positive correlation of a middle degree ($r = 0.44$, $P < 0.0001$) between IAH and PCT values ofiIntra-abdominal infections. Medium - scale correlation was also found between CRP and IAH iniIntra-abdominal infections ($r = 0.42$,$P < 0.0001$).

Moreover, we have investigated the correlation of PCT, CRP, APACHE II, MODS, SOFA, IMP, APP, FG, diuresis and fluid balance about IAH grades. The results showed a statistical significance of these parameters, and exposure of IAH yielded a predictive role of PCT and IAH in the course of the disease. There is relevant evidence that proves the PCT correlation with IAH, involving only acute pancreatitis. Berenau et al., analysed the correlation between maximum IAP values and mean PCT values in acute pancreatic patients, which was highly significant [18]. Bettina M. Rau et al., [19] has established conclusion that pancreatic patients with acute pancreatitis, with infected pancreatic necrosis and MODS or those who have died have significant association with PCT's high values compared to complications, while Bezmarevic concludes that in the first 24 hours acceptance of acute pancreatitis to determine the severity of the disease PCT has higher sensitivity and similarity to APACHE II while CRP has low sensitivity in this regard, at the same time the growth of IAP is followed by increased PCT, so there is a correlation between these parameters and have a predictive role of disease progression [20].

In our study, the PCT values were high in severe sepsis and septic shock patients. High PCT values in septic shock were also found in other studies [21] [22] [23]. Despite that CRP values are high in all IAH groups of our study; there is no significant difference between groups. Many authors conclude that patients with a severe degree of IAH manifest, evident clinical changes in cardiovascular function [24] [25] [26], splanchnic hypoperfusion [27] and acute renal failure [28] [29]. The high values of the IAP result in organ dysfunction, which results in high values of the MODS escalation [30] [31]. The development of purulent peritonitis increases the IMP degrees that correspond to the growth of the IAP [32]. In other studies, results showed that the IAH presence was associated with significant increases in the SOFA scaling indicating that the IAH has negative effects not only on the abdomen but also on the function of other organs [33] at the same time the high values ofiIntra-abdominal pressure are in correlation with high APACHE II values [33] and complied to the data from our study. Studies conducted to confirm that patients with IAH and high scores of SOFA and APACHE II have a worse clinical prognosis for hospital treatment and intensive care [33] [34] [35] [37]. Taking into account the correlation of APACHE II with PCT it has been concluded that the increase in values of this marker is related to the severity of the disease and is the early marker of sepsis [29] APACHE II shows significant PCT correlation in dysfunctional and non - dysfunctional patients, whereas CRP correlation with APACH II was not significant [28]. Similar data are also provided by Lopez et al. [34].

In our study of GII, GIII/ACS we had a decrease in the GF, APP, diuretic and fluid balance values and we have gained a distinction of statistical significance of these parameters by the IAH grades. Even in other studies, patients who did not survive had high levels of IAP and low values of APP, diuresis and fluid balance and FG [33] [37] [38]. In the research work of Kovac, it turns out that APP has a significant correlation with MODS, APACHE II and SIRS until the IAP shows no correlation with these parameters [32].

PCT and IAP transmitted before and after the operation resulted in higher values of probability of septic shock and severe sepsis have a significant difference in these parameters according to the severity of the infection, indicating that the deterioration of the overall state of the average of these parameters grows. CRP values are increased, but there is no significant difference according to the severity of the infection. Nargis findings show that PCT is more predictive than CRP in identifying and assessing the severity of sepsis even though both markers cannot differentiate infectious and non - infectious clinical syndromes [39]. In our study, we also found that PCT is more reliable in assessing the severity of the disease. PCT remains elevated in patients with severe sepsis and septic shock; this increases the risk of mortality regardless of the level [15] [39] [40].

The study performed by Sameh in 25 patients diagnosed as SIRS, sepsis, severe sepsis and septic shock with aetiology from all organs, analysed the PCT and CRP valued and its data resulted that CRP does not show any degree of differentiation of severity of sepsis [41]. Similar data was also given in the study conducted by Castelli [42] that corresponds to the data from our research.

In conclusion, the increase in IAP is followed by increased PCT and CRP values. In this study, we have identified the correlation in the values of PCT and CRP toiIntra-abdominal infections where IAH is present. PCT results are high in all cases with IAH, and there is a significant statistical significance by IAH grades in the first 24 hours. However, CRP results are high but without a significant difference to IAH grades. High PCT and IAP values are evident in severe sepsis and septic shocks that are correlated with low FG, APP, diuresis and fluid balance and high mortality rate scores. The role of PCT iniIntra-abdominal infections is of greater diagnostic and predictive value compared

to CRP values; however, the role of CRP remains important for the identification of other clinical circumstances.

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A Study of Selenium in Leprosy

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Abstract

INTRODUCTION: Leprosy is a chronic infection caused by *Mycobacterium leprae*. Selenium, on the other hand, is a substance, which is needed for its protective role against microorganism infection.

AIM: This study aims to know the association between selenium serum levels with bacteriological index.

METHODS: This is an analytical cross-sectional study model. Sampling was done with consecutive sampling method in Pirngadi General Hospital, Lau Simomo Leprosy Hospital and H. Adam Malik General Hospital. Samples were taken from patients' venous blood serum then selenium levels were measured.

RESULTS: This study found 30 leprosy patients consisted of 19 patients with paucibacillary (PB) leprosy and 11 patients with multibacillary (MB) leprosy. Selenium serum levels of patients with PB leprosy (mean = 97.16 µg/dL) were found to be significantly higher than MB leprosy (mean = 77.27 µg/dL) with p = 0.008 using t-test. The negative correlation between selenium serum levels with bacterial index in patients with leprosy was also found in this study using Spearman's rho test (r = - 0.499, p = 0.005).

CONCLUSIONS: Selenium serum levels of patients with PB leprosy are higher than patients with MB leprosy, and high bacteriological index in patients with leprosy were correlated with low selenium serum levels.

Introduction

Leprosy, also known as Hansen's disease is a chronic infection caused by *M. leprae* bacteria which primarily targets skin and peripheral nerves [1] [2]. Leprosy is common in developing countries [3]. According to World Health Organization (WHO) report in 2016 that received from 143 countries, the prevalence of leprosy was registered as 0.23 per 10.000 populations with 171.948 leprosy cases on treatment. During the year, 214.783 new cases (2, 9 per 100.000 populations) were reported globally. A country can be classified as leprosy endemic country if the mean prevalence is found more than 1 case per 10.000 inhabitants (10 cases per 100.000 inhabitants). According to the criteria, from highest to lowest, India, Brazil, Indonesia, Ethiopia and Bangladesh are the five leprosy endemic countries with most leprosy new cases in the world [4] [5].

Agent – host - environment model can be used to explain numerous factors that affect the natural history of Hansen's disease. *M. leprae* serves as the agent factor. Host factors include age, gender, genetics, nutritional status, and immunity levels. Environmental factors include living and migrating to leprosy endemic areas [6] [7].

Nutrition holds a crucial role in affecting both cellular and humoral immune system. Trace element deficiency may cause inadequate host response to the infectious pathogens [8].

Selenium is one of the trace elements that hold a crucial role in the immune system and

protection against free radicals. Selenium is a biological antioxidant. Selenium is known to have a role in glutathione peroxidase activation – the main enzyme to defend against oxidative stress [9]. Glutathione catalyses hydrogen peroxide and organic hydroperoxide reduction, and this can protect the fat and other tissues against oxidative damage [8].

This study aims to know the association between selenium serum levels with bacteriological index.

Methods

This is an analytical cross-sectional study model and was held from June until November 2017 at Pirngadi General Hospital, Lau Simomo Leprosy Hospital and H. Adam Malik General Hospital. The inclusion criteria consist of leprosy patient, above 15 years old, and the exclusion criteria are patient with a history of antioxidant consumption. Samples were taken from patient's venous blood serum then selenium levels were measured using ICP - MS (Introductive Couple Plasma Mass Spectrometry) method with Agilent 7700 machine. Slit - skin smears were taken to measure the bacteriological index.

Samples were taken from two or three locations including both earlobes and active skin lesion. Staining was done with Ziehl - Neelsen method. The bacteriological index was then scored according to Ridley logarithmic scale.

The collected data then analysed using Kolmogorov Smirnov to evaluate the normality of data distribution. The mean selenium level in PB and MB group was then compared and analysed using T-test. Spearman rho was used to see the correlation between selenium serum levels with bacteriological index.

Results

Leprosy patient's characteristics

This study has found 30 samples that satisfied the inclusion and exclusion criteria. Samples consisted of 19 (63.3%) paucibacillary (PB) leprosy patients and 11 (36.7%) multibacillary (MB) leprosy patients.

Based on the bacteriological index distribution, this study found most cases have 0 (negative) bacteriological indexes at 19 cases (63.3%). Characteristics of leprosy patients are summarised in Table 1.

Table 1: Leprosy patient's characteristics

No.	Characteristics		Amount (n)	(%)
1.	Gender			
	-	Male	20	66.7
	-	Female	10	33.3
2.	Age group			
	-	16-35	12	40
	-	36-55	11	36.7
	-	56-75	7	23.3
3.	Leprosy classification			
	-	MB	11	36.7
	-	PB	19	66.3
4.	Bacteriological index			
	-	0	19	63.3
	-	+1	6	20
	-	+2	2	6.7
	-	+3	3	10

Selenium serum levels in Paucibacillary (PB) leprosy patients and Multibacillary (MB) patients

The selenium serum levels mean found in this study were 97.21 µg/dl for PB leprosy patients and 77.27 µg/dl for MB leprosy patients. The mean difference between two groups was 19.94 µg/dl. A t-test was then performed to know the selenium serum levels difference between the two groups. The test found a significant difference between selenium serum levels of PB leprosy patients and MB leprosy patients. Thus it can be concluded that selenium serum levels in PB leprosy patients are higher than selenium serum levels in MB leprosy patients.

Correlation between selenium serum levels with bacterial index in leprosy patients

Spearman's rho test was performed to see the correlation between selenium serum levels with bacteriological index. Negative correlation between selenium serum levels with bacteriological index in leprosy patients was then found ($r = -0.499$; $p = 0.005$). It can be concluded that the higher the bacteriological index is, the lower selenium serum level will be (63.3%)

Discussion

According to the gender distribution, this study found more male leprosy patients (20 people, 66.7%) compared to female leprosy patients (10 people, 33.3%). This finding is similar to a study done by Miranzi (2010) in Brazil [10] where 455 leprosy cases 55.4% were found in the male. Several pieces of evidence hinted a causal relationship between the region with diagnosed and treated leprosy patients gender ratio. In Asian regions, more males are registered as leprosy patients compared to females while in African regions more females are registered as leprosy patients compared to males [11].

Most cases in this study were found within the 16-35 years old age group at 12 cases (40%) followed by 36-55 years old age group at 11 cases (36.7%). A study by Verkevisser in Brazil found that most of the leprosy cases within the 34 - 49 age group at 31.4%. This is important since people from this age group are economically productive and thus have a higher transmission risk [11].

A study by Ramakrishnan et al. in India found selenium levels in patients with lung tuberculosis were lower (66 µg/dl) than healthy controls (113.1 µg/dl) [12]. Another study was done by Lettow et al. in Malawi which involved 579 lung tuberculosis patients with HIV and 222 lung tuberculosis patients without HIV found selenium deficiency in 85% of the patients with lung tuberculosis without HIV and 87% of the patients with HIV [13]. Selenium has long been recognised for its wide spectrum of action over the cellular and humoral system and has been demonstrated to regulate levels of interleukins, thus affecting susceptibility to bacterial infection [9].

Moraes et al., do a study about the association between selenium levels with bacteriological test conversion during anti-tuberculosis treatment. It was found that high selenium levels after 60 days treatment with anti-tuberculosis medication was associated with bacteriological test conversion in patients with lung tuberculosis [14]. Another study also showed that vitamin E and selenium administration might lower oxidative stress and heighten antioxidant capacity in patients with lung tuberculosis [15]. Selenium supplementation also may suppress tumour necrosis factor and its receptors. It was the hypothesised that selenium supplementation may contribute to elimination and/or suppression of mycobacterial diseases [16].

It can be concluded from this study that lower selenium serum levels were found more within MB leprosy patients compared to PB leprosy patients. Higher bacteriological index in leprosy patients was also correlated with lower selenium serum levels. Thus, selenium serum levels investigation might have a prognostic value to evaluate the condition of leprosy patients. Further investigations are needed however to assess the efficacy of selenium administration in patients with leprosy.

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Thyroid Function and 25 (OH) Vitamin D Level among Sudanese Women in Early Pregnancy

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Abstract

AIM: A cross-sectional study was conducted at Saad Abualila Hospital (Khartoum, Sudan) to evaluate the vitamin D levels and thyroid function among pregnant Sudanese women (132) in early pregnancy.

METHODS: A cross-sectional study was conducted at Saad Abualila hospital (Khartoum, Sudan) during the period from March to July 2015. Women who were in early pregnancy with a singleton pregnancy were approached to participate in the study after signing informed consent. A sample size of 132 participants was calculated guided by the normal interval of thyroid function in Sudanese women in the first trimester and not the level of 25(OH) vitamin D. The 25 - hydroxyvitamin D (25 (OH) vitamins levels were measured using an electrochemiluminescence immunoassay on an Elecsys 2010 Analyzer (Roche Diagnostics, Mannheim, Germany).

RESULTS: The mean (SD) of age, gravidity and gestational age was 27.6 (5.5) years, 2.2 (1.6) and 10.4 (2.2) weeks, respectively. The mean (SD) of the body mass index (BMI) and haemoglobin was 27.1 (5.2) kg/m^2 and 10.8 (1.1) g/dl, respectively. Median (interquartile) values of TSH, FT3, and FT4 were 1.164 IU/ml (0.079 - 2.177 IU/ml), 4.639 nmol/l (3.843 - 6.562 nmol/l), and 16.86 pmol/l (13.02 - 31.48 pmol/l), respectively. There was no significant correlation between vitamin D levels and TSH, FT3 and FT4

CONCLUSION: There is no correlation between 25 (OH) vitamin D levels and thyroid function during early pregnancy among Sudanese pregnant women, despite prevalent vitamin D deficiency among these women.

Introduction

Vitamin D is a fat-soluble vitamin and a steroid hormone precursor, which is primarily synthesized in the skin after exposure to ultraviolet B radiation. The liver is the first organ where hydroxylation occurs to produce 25 - hydroxyvitamin D (25(OH) D). Further hydroxylation continues mainly in the kidneys to produce the active form 1, 25 - dihydroxy vitamin D (1, 25(OH) 2D), besides the placenta and several other target organs [1]. In fact, less than 10% of vitamin D is derived from main dietary sources such as dairy, eggs, fish and meat [2] [3] [4]. Moreover, vitamin D has relatively durable stability over several weeks, and approximately 99% of circulating 25(OH) D3 is bound to vitamin D - binding proteins. Interestingly, its gradual oscillation depends on solar radiation rather than on vitamin D precursors that are gained from food items [5].

Vitamin D has many vital functions such as endocrine, autocrine (the activity of vitamin D_3 arises from 1,25D synthesized within those cells), paracrine (1,25D is synthesized in one cell type and acts within adjacent cells), regulation of gene expression (it shares many pathways with p53), cell differentiation and proliferation [6] [7] [8]. Vitamin D receptors are found in many cells and tissues of the human body that are responsible for regulating the expression of more than 1000 genes in humans [9]. Allelic variants of the vitamin D - binding protein (DBP) gene enhance susceptibility to Graves' disease but not to Hashimoto's thyroiditis, which expresses the endocrine role of vitamin D [10]. In contrast to this, some studies proposed an association between vitamin D deficiency and Hashimoto's thyroiditis where a higher prevalence of vitamin D deficiency was reported among these patients [11] [12] [13]. At the same time, a significantly higher prevalence of vitamin D deficiency has been reported among

patients with autoimmune thyroid disorders, hypothyroidism, overt hypothyroidism and Graves' disease [14]. However, another study showed no significant relationship between non - autoimmune thyrotoxicosis and vitamin D status during pregnancy [15].

Mazokopakis *et al.* observed an inverse correlation between low serum 25(OH) D levels in euthyroid patients with Hashimoto's thyroiditis who had high serum anti-thyroid peroxidase (TPO) antibodies [16]. Despite the fact that many studies have evaluated the role of vitamin D in thyroid diseases, few studies explored the effects of 25 (OH)D in association with thyroid function in pregnancy and maternal and foetal outcomes [17] [18]. Some data focused on the adverse events of the coincidental findings of both vitamin D deficiency and thyroid disorders during pregnancy: increased risk of preeclampsia, gestational hypertension, gestational diabetes mellitus, premature delivery and low birth weight [19] [20] [21] [22]. In vitro and in vivo studies propose an increased response to 1, 25(OH) 2D in the presence of T3 in cultured anterior pituitary cells.

Moreover, an increased level of TSH is observed after acute administration of 1, 25(OH) 2D [23]. One study focused on this relationship and documented that high vitamin D status was associated with low circulating TSH in a younger group of patients [24]. On the other hand, Glinoer noted the enhancement of thyroid hormones and induced partial suppression of serum TSH in response to the sharp increase of human chorionic gonadotropin in the 1st trimester [25]. Another study from Sudan reported a suppressive effect of pregnancy on thyroid parameters TSH, FT4 and T3(26).

Due to a higher global prevalence of vitamin D deficiency, increasing concern has been raised on maternal vitamin D deficiency and possible maternal and perinatal adverse effects [18] [27] [28]. There is a high prevalence of vitamin D deficiency (vitamin D level ≤ 20 ng/ml) among pregnant women in some tropical areas, e.g., 29% and 18.9 of women in Nigeria and southern China, respectively [29] [30]. There is no published data on vitamin D and thyroid function in Sudan. Hence, the current study was conducted to assess the association of thyroid function and vitamin D levels among Sudanese women in early pregnancy.

Method

A cross-sectional study was conducted at Saad Abualila hospital (Khartoum, Sudan) during the period from March to July 2015. Women who were in early pregnancy with a singleton pregnancy were approached to participate in the study after signing informed consent. A sample size of 132 participants was calculated guided by the normal interval of thyroid function in Sudanese women in the first trimester and not the level of 25(OH) vitamin D (no previous data). This sample size has over 80% power to detect a difference of 5% at $\alpha = 0.05$. We assumed that 10% of the women might not respond or might have incomplete data. Exclusion criteria included chronic diseases of the liver and kidney, previous gastrointestinal surgery, pulmonary tuberculosis, lymphoma, primary hyperparathyroidism, hyperthyroidism, epilepsy on anticonvulsants therapy, intake of vitamin D within the last six months or on medications that could interfere with its metabolism such as glucocorticoids, and current anticonvulsant therapy.

Sociodemographic and obstetric history were gathered using a questionnaire. The height and weight were measured using conventional methods and were used to calculate the body mass index (BMI) by using the formula: weight in kilograms (kg) divided by the square of the height in metres (m^2). A blood sample was collected in a gold - top serum separator tube and allowed to clot. The samples were centrifuged at 1100 - 2000 g for 10 minutes. Serum then was separated from cells immediately and refrigerated at temperature 2 to 8°C before processing it. Grossly haemolysed, lipemic or samples containing particulate material were rejected. The 25 - hydroxyvitamin D (25 (OH) vitamins levels were measured using an electrochemiluminescence immunoassay on an Elecsys 2010 Analyzer (Roche Diagnostics, Mannheim, Germany). The normal level of 25 (OH) D is 20 ng/ml or above [31]. Thyroid function tests (TSH, T3and T4) were obtained using commercially available kits by Roche Elecsys Modular Analytics Cobas e411 utilising electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Complete blood count was checked to assess haemoglobin (Hb) levels.

Ethics

The study received ethical approval from the board of the Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Khartoum, Sudan.

Statistics

Data were entered into a computer and SPSS for Windows was used for data analyses. Continuous data were checked for normality using the Shapiro - Wilk test. Data were expressed as proportions: mean (SD) and median (interquartile). Correlation (Pearson and Spearman) were performed. $P < 0.05$ was considered statistically significant.

Results

One hundred – thirty - two women were enrolled in the study. The mean (SD) of age, gravidity and gestational age was 27.6 (5.5) years, 2.2 (1.6) and 10.4 (2.2) weeks, respectively. The majority (81.8%) of these women had urban residence and were housewives (75.8). The mean (SD) of the BMI and haemoglobin were 27.1 (5.2) kg/m^2 and 10.8 (1.1) g/dl, respectively. The mean (SD) or median (interquartile) of TSH, FT3, FT4 and vitamin level are shown in Table 1.

Table 1: The level of thyroid hormones and 25 (OH) vitamin D level in Sudanese women in early pregnancy

Variables	
	5-95%, mean (SD) of
FT3, pmol/l	1.483–2.670, 2.022 (0.339)
FT4, pmol/l	0.760–1.390, 1.072(1.972)
	5-95%, median (interquartile) of
TSH, m iU/l	0.579–3.424, 1.684 (1.163–2.104)
25 (OH) vitamin D, ng/ml	5.3–16.1, 8.4(7.2– 11.1)

Except for one woman, all the participants (99.2%) demonstrated vitamin D deficiency. There is no correlation between 25 (OH) vitamin D, thyroid functions and BMI, Table 2.

Table 2: Correlations between thyroid functions, BMI and 25 (OH) vitamin D

Variable	FT3		FT4		TSH		BMI	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
FT3			0.001	0.992	0.128	0.144	0.043	0.620
FT4					- 0.122	0.202	-0.059	0.502
TSH							0.033	0.711
25 (OH) vitamin D	0.010	0.910	0.133	0.129	- 0.003	0.970	- 0.156	0.075

Discussion

The current study showed no significant association between vitamin D levels and thyroid functions among pregnant Sudanese women during the 1st trimester. This is in concordance with a previous study that was conducted among pregnant women in Northern China [32]. In the latter study, a high prevalence (96%) of vitamin D deficiency during the 1st trimester was reported [32]. Likewise, a non - significant difference between vitamin D deficiency and thyroid antibodies status was reported in a case-control study that recruited 531 pregnant women and 238 age-matched, non - pregnant women as a control group [33]. Another study showed no correlation between 25 – Hydroxyvitamin D, FT4 and FT3 hormone during pregnancy, but a significant correlation was observed among pregnant women with higher and sufficient levels of vitamin D (> 30.0 ng/ml) and lower TSH [34]. These may be explained by the specific course of pregnancy that reflects the state of immune tolerance as the antithyroid autoantibody titers reduce by at least 50% from the 1st to the 3rd trimester [35].

Thus, a weak association between 25(OH) D and thyroid antibodies may result, leading to a non - significant relationship [32]. Hence, researchers speculated that both 25(OH) D and thyroid dysfunction might work independently and contribute to some of the same adverse effects during pregnancy [32]. We also propose that a higher level of human chorionic gonadotropin in the 1st trimester that influences TSH may be considered another contributing factor to weaken such coincidental effects. Moreover, no association was reported between vitamin D deficiency in non - pregnant women in both cases and control group, the hypothyroid and euthyroid subjects [36]. On the other hand, a significant correlation between vitamin D deficiency and all thyroid parameters (TSH, T4 and T3) have been documented among pregnant women in Italy [37].

Furthermore, a significant correlation between vitamin D and TSH has been observed among pregnant women with a sufficient level of vitamin D (> 30 ng/ml) [34]. A recent population-based health survey reported a higher prevalence of vitamin D deficiency and insufficiency in thyroglobulin antibodies (TgAb) positive cases which were 78.3% and 20% respectively [38]. Vitamin D deficiency has been reported as a risk factor for autoimmune thyroiditis and thyroid hypofunction [6] [39]. This may be explained by the unique immunomodulatory effect of 1, 25 - (OH) 2D3 which is observed on T - lymphocyte function, antigen presenting cells and stimulated phagocytosis. It, therefore, inhibits the cytodestructive ability of T helper type - 1(Th1) lymphocytes, and enhances T helper type - 2(Th2) cytokine (Interleukin - 4) production [40]. Both vitamin D and thyroid hormone share the same steroid hormone receptors [5].

Nevertheless, there is some evidence that links vitamin D receptor gene polymorphisms with autoimmune thyroid diseases (AITD) [6]. The mutation of genes encoding for tissue hydroxylases and Vitamin D receptor additionally carries a potential risk of developing thyroid cancer [41]. In a case-control study, 53 patients with gestational transient thyrotoxicosis and 35 healthy pregnant women were recruited, and vitamin D levels were significantly lower in cases when compared to the controls (11.1 ± 7.7 and 16.5 ± 0.5 ng/mL, respectively) [42]. A previous study documented an association between pronounced decreased levels of 25(OH) D3 and Graves' disease, in addition to an inverse correlation between 25(OH) D3 levels and thyroid gland volume [43]. Being a female may harbour a genetic risk for thyroid dysfunction, and global vitamin deficiency may influence the outcome of some studies. This is supported by a recent study that enrolled a total

number of 1714 subjects (females = 1197 and males = 517) and showed significantly higher serum TSH levels, higher thyroid antibodies titers and lower serum 25(OH) vitamin D levels in females compared to males [38].

The active calcitriol is promoted as a translocation regulator for T3 in the cerebellum by improving the binding capacity of the cytosolic T3 - binding protein [44]. Moreover, it enhances TSH secretion of thyrotropin at the pituitary level [45]. The placental oestrogen stimulates Thyroxine Binding Globulin (TBG) synthesis [6]. The role of thyroid hormones is to stimulate intrauterine foetal growth, which is evident during the second half of gestation and has an influence on foetal metabolism [37]. Vitamin D deficiency has negative effects on thyroid functions, and when both coincide together during pregnancy, imminent harm may come to both mother and her foetus; hence, correction of both disorders is recommended to minimise risk. The limitations of this study are the seasonal variation for vitamin D levels and some laboratory tests that are not included, e.g., calcium, phosphorous, parathyroid hormones and thyroid antibodies.

In conclusion, our study showed no significant association between vitamin D deficiency and thyroid function during the 1st trimester among Sudanese pregnant women despite the higher prevalence of vitamin D deficiency. We recommend further studies in this area.

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Physiotherapy Effects in Gait Speed in Patients with Knee Osteoarthritis

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Abstract

BACKGROUND: Knee osteoarthritis is a chronic degenerative disease, known as the most common cause of difficulty walking in older adults and subsequently is associated with slow walking. Also one of the main symptoms is a degenerative and mechanics type of pain. Pain is very noticeable while walking in rugged terrain, during ascent and descent of stairs, when changing from sitting to standing position as well as staying in one position for a long time. Many studies have shown that the strength of the quadriceps femoris muscle can affect gait, by improving or weakening it. Kinesio Tape is a physiotherapeutic technique, which reduces pain and increases muscular strength by irritating the skin receptors.

AIM: The aims of this study was first to verify if the application of Kinesio Tape on quadriceps femoris muscle increases gait speed in patients with knee osteoarthritis and secondly if applying Kinesio Tape on quadriceps femoris muscle reduces pain while walking.

METHOD: Seventy-four patients with primary knee osteoarthritis, aged 50 - 73 years, participated in this study. Firstly we observed the change of gait speed, while walking for 10 meters at normal speed for each patient, before, one day and three days after the application of Kinesio Tape on quadriceps femoris muscle, with the help of the 10 - meter walk test. Secondly, we observed the change of pain, while walking for 10 meters at normal speed for each patient, before, one day and three days after the application, with the help of Numerical Pain Rating Scale - NRS.

RESULTS: Our results indicated that there was a significant increase in gait speed while walking for 10 meters one day and also three days after application of Kinesio Tape on quadriceps femoris muscle. Also, there was a significant reduction of pain level 1 and 3 days after application of Kinesio Tape, compared to the level of pain before its application.

CONCLUSIONS: Our results indicated that there was a significant decrease in pain and increase of gait speed while walking for 10 meters. Kinesio Tape can be used in patients with knee osteoarthritis, especially when changing walking stereotypes is a long-term goal of the treatment.

Introduction

Osteoarthritis is a widespread, slowly developing disease, with a high prevalence increasing with age. The most common large joints involved in the disease are the knees, where the disease is particularly disabling because of difficulty in rising from a chair, climbing stairs, kneeling, standing and most important walking. These limitations are partly due to muscle weakness, especially quadriceps femoris muscle [1] [2] [3] [4]. It has been suggested that functional ability is also affected by poor proprioception [5] [6] [7] [8] [9] [10] [11].

Patients with knee osteoarthritis have a problem walking and tend to walk slower than controls. It is shown that knee osteoarthritis is the most common cause of difficulty walking in older adults [12] [13] and subsequently is associated with slow walking [14] [15]. Previous cross-sectional studies report that people with both radiographic knee osteoarthritis and knee pain have slower walking speed than healthy age-matched controls [15] [16] [17].

In knee osteoarthritis, decreased walking speed is associated with joint space narrowing [18], increased concentrations of inflammation mediators [19], pain [20] and also and quadriceps muscle weakness [21] [22]. Increased joint stresses occur with faster-walking speeds [23] [24], and repetitive high-level dynamic joint loading has been shown to contribute to chondrocyte death [25] and the development of osteoarthritis in animal models [26]. As with healthy individuals, the increase of walking speed can mean an additional joint overload in elderly

patients with osteoarthritis, which was also shown for elderly persons without osteoarthritis [28] [29]. Faster walking speed in combination with abnormal joint biomechanics may further amplify dynamic joint loading [23] and may accelerate joint degeneration. Decreasing walking speed has been suggested as a mechanism used by individuals with knee pathologies to reduce loading and pain in the medial compartment of the knee [27].

Lay et al. [30] reported that when walking at the same speed, hip, knee, and ankle (plantar flexor) extensor muscle activations increased during uphill walking, but only the knee extensor muscle (quadriceps muscle) activations increased during downhill walking. Main contributors to progression and support during gait are the quadriceps femoris, gluteus maximus and plantar flexors. Quadriceps femoris weakness, in particular, has been linked to functional impairment such as increased fall risk and slower walking speed, also is one of the earliest and most common symptoms of osteoarthritis [31] [32] [33].

The aim of this study was verify if the application of Kinesio Tape on quadriceps muscle changes walking speed and pain while walking for 10 meters at normal speed, in patients with knee osteoarthritis before the application of Kinesio Tape, a day after the application of Kinesio Tape and three days after the application of Kinesio Tape on quadriceps femoris muscle.

Patients and Methods

The subjects (n = 74), aged 50 – 73 years (mean age 61.5), 67% of whom were female, were consecutive outpatients with a clinical diagnosis of primary unilateral knee osteoarthritis made by a rheumatologist. The main criterion for the selection of the subjects in this study was the diagnosis of knee osteoarthritis by X-ray. Criteria for excluding subjects in the study were other musculoskeletal diseases, total knee replacement, significant hip or spinal arthritis, neurological diseases and diseases that affect balance and coordination. The subjects were not in medical treatment. All of the subjects signed a written consent to participate in the study voluntarily.

Kinesio Tape (KT) was applied with a tonus regulation technique also called muscle technique on quadriceps femoris muscle. We measured the tape length in the maximal stretched position of the tissue. The application was made with the patient in this maximal stretched position. The tape was applied without stretch following the course of the muscle borders from one insertion to the opposite one.

We observed the change of walking speed, while walking for 10 meters at normal speed for each patient, before, a day after the application and three days after the application of KT on quadriceps femoris muscle, with the help of a 10 meter walk test, where we measured and marked a 10 - metre walkway adding a mark at 2 - metres and at 8 - metres. The patient performed three trials, and we calculate the average of three trials [35]. Also we observed the change of pain, while walking for 10 meters at normal speed for each patient, before, a day after the application and three days after the application of KT on quadriceps femoris muscle, with the help of numerical pain rating scale - NRS. The worse knee, as assessed by X - ray was the “index” knee. Pain was assessed by numerical pain rating scale (NRS), by instructing the patient to choose a number from 0 to 10 that best describes their current pain. 0 would mean “no pain” and 10 would mean “worst possible pain” [34].

Statistical Analysis

Continuous variables were presented as mean and standard deviation: mean ± SD (standard deviation). Categorical variables are presented as actual numbers (n) and percentages (%). Chi-square analysis was used to compare frequencies between groups and Student t-test, one - way ANOVA or non - parametric tests were used when necessary for quantitative analysis of the variables. The analysis was conducted using the SPSS (statistical software statistics package for social scientists) version 15.0. Statistical significance was considered to be the value of $P \leq 0.05$.

Results

Seventy-four out-patients with a clinical diagnosis of primary knee osteoarthritis participated in this study, mean age of the participants was 61.5 (range: 50 - 73). The worse knee as assessed by X-ray was the “index” knee.

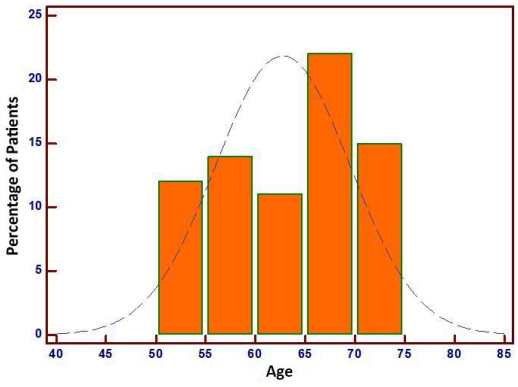

Figure 1: Age distribution histogram of patients

Table 1: Data results on gait speed in seconds before the application of KT (10MWT Before KT), one day after the application of KT (10 MWT 1 Day after KT) and three days after the application of KT (10 MWT 3 Days after KT) on quadriceps femoris muscle

	Nr.	Mean	SD	Minimum Value	Maximum Value
10 MWT Before KT	74	9.917	2.3458	6.173	16.277
10 MWT 1 day after KT	74	9.462	2.2734	6.160	15.847
10 MWT 3 days after KT	74	6.319	1.6274	4.123	10.787

The results show that there is a significant increase in gait speed as patients complete the route along 10 meters in less time 1 day and 3 days after KT application. 10 MWT before KT application compared to 10MWT 1 day after KT application has no significant change, P = 0.23. 10 MWT before KT application compared to 10MWT 3 days after application of KT has a significant change, P < 0.0001. Also, 10MWT 1 day after KT application compared to 10MWT 3 days after KT application has significant change, P < 0.0001.

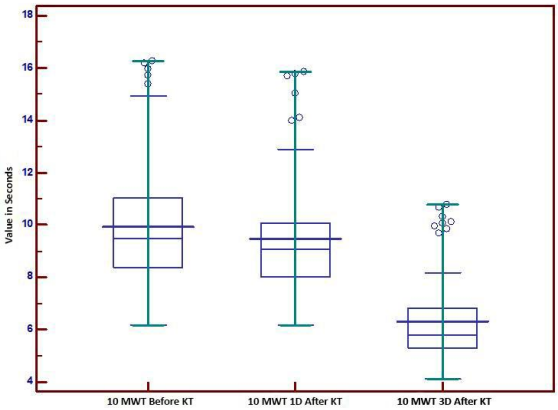

Figure 2: Comparison of gait speed in seconds before the application of KT (10MWT Before KT), one day after the application of KT (10 MWT 1 D After KT) and three days after the application of KT (10 MWT 3 D After KT) on quadriceps femoris muscle

The results show that there is a significant reduction in pain level 1 and 3 days after KT application, compared with the level of pain before its application. The degree of pain reported before KT application compared to the reported pain level 1 day after KT application has a significant change, P < 0.0001.

Table 2: Data results on pain level according to NRS before KT application, one day after KT application and three days after KT application on quadriceps femoris muscle

	Nr.	Mean	SD	Minimum Value	Maximum Value
NRS before KT	74	6.514	1.1849	5.000	8.000
NRS 1 day after KT	74	5.554	0.9951	4.000	8.000
NRS 3 days after KT	74	3.243	0.7730	2.000	4.000

The pain level reported before KT application compared to the reported pain level 3 days after the application of KT has a significant change, P < 0.0001. Also, the level of pain reported 1 day after KT application compared to the reported pain level 3 days after KT application has significant change, P < 0.0001.

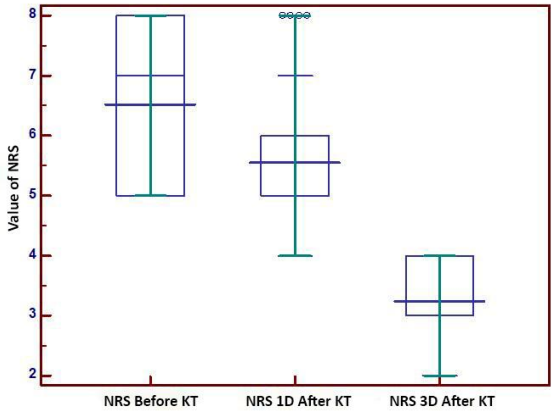

Figure 3: Comparison of pain level results according to NRS before KT (NRS before KT), one day after KT (NRS 1D after KT) and three days after KT (NRS 3D After KT) application on quadriceps femoris muscle

Discussion

Lack of information about the impact of elastic therapeutic tape in gait speed in this diagnosis led us to carry out this research. Our objective was to determine whether the application of Kinesio Tape on quadriceps muscle in patients with knee osteoarthritis will lead to increasing gait speed while walking a 10-meter distance at a normal speed.

The results of this study showed a significant increase in gait speed during walking one day and three days after applying Kinesio Tape on quadriceps femoris muscle. In graphic1 is shown that most of the patients finish the 10-meter walk test in a shorter time after applying Kinesio tape on quadriceps muscle a day and also three days after the application. However, a significant decrease in pain intensity was shown, during walking, three days after applying the Kinesio Tape. Similar findings have been reported elsewhere. Kaya et al. [47] studied 55 patients with shoulder impingement syndrome treated by Kinesio Tape or local modalities and found that although the immediate effect of Kinesio Tape is greater than the local modalities, Kinesio Tape was similarly effective at the second week of the treatment.

Based on these results, it can be inferred that applying Kinesio tape facilitated muscle activation in the indexed knee on patient increased gait speed and decreased the time needed to perform the 10-meter walk test. This suggests that applying Kinesio Tape leads to improvement in walking speed through muscle facilitation in the indexed knee [36]. This is because Kinesio Tape effectively stimulated the proprioceptive sense, muscle spindles, Golgi tendons,

etc., and strengthened muscles in the affected parts [37]. These results were in agreement with the results of previous studies, which reported that Kinesio Tape increases muscle activity, restricts excessive movement of the joint and increases gait speed [38] [39].

However other studies did not find significant differences immediately after Kinesio tape application [40] [41]. Chang et al. [42] found no change in grip strength immediately after applying Kinesio tape in healthy people. Lins et al. [43] evaluated the effects of Kinesio tape application on the activity of the vastus lateralis, rectus femoris, and vastus medialis muscles of healthy women who exercised and found no significant effects.

Słupik et al. [44] evaluated the effects of applying KT over the vastus medialis and found no change in muscle activity 10 minutes post -taping but, similar to us; they found increased muscle activity 24 hours after Kinesio tape application. The difference between these results may be due to different forms and tensions of Kinesio tape application. Different Kinesio tape techniques can provide different tactile stimulation intensities [37].

Kase et al. [45] and Thelen et al. [46] however, recommend at least three daily actions of elastic therapeutic tape. Kase et al. mention that three days after the application of Kinesio Tape can occur soft tissue changes, improvement of muscle function, increase of blood circulation and lymphatic drainage. Thelen et al. found that after three days of Kinesio Tape application was shown a significant decrease in the functional shoulder joint pain and increase of movement.

Limitations in this study were the sample size, with a greater sample size we could get better results. In this study, the effect of Kinesio Tape in increasing gait speed in knee osteoarthritis was statistically significant. Further studies are needed to investigate the effect of Kinesio Tape in gait speed on knee osteoarthritis.

In conclusion, there seems to be a significant increase of gaits Speed and a decrease of time needed to accomplish the 10-meter walk test one day and also three days after applying Kinesio Tape on quadriceps femoris muscle. Also, there was a significant decrease in pain one day and three days after applying Kinesio Tape on quadriceps femoris muscle.

Kinesio Tape can be used in patients with knee osteoarthritis, especially when changing walking stereotypes is a long-term goal of the treatment. More clinical research is needed to investigate the effect of Kinesio Tape in gait speed on knee osteoarthritis.

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Clinical Science

Pharmacotherapy Evaluation and Utilization in Coronary Artery Bypass Grafting Patients in Kosovo during the Period 2016-2017

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Abstract

BACKGROUND: Coronary Artery Bypass Grafting (CABG) is realised in patients with critical or advanced disease of coronary arteries. There are different pharmacotherapeutic approaches which are used as management, treatment and preventive therapy in cardiovascular disease or related comorbidities. Performing a successful surgery, pharmacotherapy, and increase of bypass patency rate remains a serious challenge.

AIM: This study aims to analyse the patient characteristics undergoing CABG and evaluation of their drug utilisation rate and daily dosages in the perioperative period.

MATERIAL AND METHODS: Data were collected from 102 patients in the period 2016-2017 and detailed therapeutic prescription and dosages, patient characteristics were analysed before the operation, after the operation and visit after operation in the Clinic of Cardiac surgery-University Clinical Center of Kosovo.

RESULTS: Our findings had shown that patients provided to have normal biochemical parameters in the clinic before the operation, and were related to cardiovascular diseases and comorbidities and risk factors with mainly elective intervention. The, however, higher utilisation of cardiovascular drugs such as beta blockers, diuretics, anticoagulants, statins and lower calcium blockers, ACEi, ARBs, hydrochlorothiazide, amiodarone were founded. ARBs, beta blockers, statins, nitrates and nadroparin utilisation decreased after operation and visit after the operation, whereas amiodarone only in the visit after the operation. Diuretics are increased after the operation which decreases in the visit after the operation. Regarding the daily dosage, only metoprolol was increased in the visit after operation ($P < 0.001$) and visit after operation ($P < 0.05$) whereas losartan and furosemide were increased ($P < 0.01$) and ($P < 0.05$) respectively.

CONCLUSION: The study showed that beta blockers, statins, aspirin, nitrates (before the operation), furosemide and spironolactone are the most utilised drugs. However, we found low utilisation rate for ACEi, ARBs, clopidogrel, nadroparin, warfarin, xanthines, amiodarone, calcium blockers. Daily dosages were different compared to before CABG only in metoprolol, losartan, and furosemide.

Introduction

Cardiovascular diseases are the biggest cause of mortality and are mostly related to the coronary heart being also higher rate cause of morbidity cross-linked with ischemic heart disease and neurologic damages from cerebral haemorrhages [1] [2] [3]. In atherosclerosis, the main mechanism of worsening of the disease remains to inflammatory processes during the atherogenesis [4]. Also, lipid deposits and oxidised phospholipids are involved in many processes such as endothelium dysfunction, activation of adhesive molecules, chemotactic factors which promote interactions between leukocytes and endothelium, tissue factor releases and activation of coagulation cascades up to atherothrombotic formation [5] [6].

Epidemiologic studies provided that diabetes mellitus, hypertension, and lifestyle with high lipid intake, stress, and sedentary life are the main triggers for the appearance of the disease [7]. Due to this pharmacotherapeutic approaches with antithrombotic, antiaggregant, hypolipidemic, anti-inflammatory, vasorelaxant, antihypertensive, percutaneous coronary interventions and cardiovascular surgeries including coronary artery bypass grafting (CABG)

regarding prevention and treatment of cardiovascular diseases, atherosclerosis and endothelial dysfunction and critically advanced stages of coronary artery diseases are improving [8] [9].

Patients with stenosed arteries that undergo CABG are mostly realized with saphenous vein (SV), mammary or radial artery grafts and provides improvement of angina symptoms, better quality of life and survival rates [10], while there is also difference between the type of grafts in terms of susceptibility to atherosclerosis, occlusion, and failure of grafts which mostly included SV as more sensitive to these pathophysiologic processes [11]. Therefore based on these facts among the main problems which are still appeared in patients undergoing CABG are graft failure and occlusion also related with the atherothrombotic formation, increased vasospastic agents which play a role in early and late phases of these interventions [12] [13]. The survival rate is higher in left internal mammary artery grafts and radial artery [14] [15].

There are different study approaches regarding management of perioperative symptoms and diseases by interfering in graft tissues pathophysiology which increase CABG patency rate and reduce operation complications. These groups of patients are recommended to use multiple pharmacotherapeutic agents to prevent perioperative complications [8]. Main therapies are antithrombotic, antiaggregant and anticoagulant drugs such as aspirin, clopidogrel, tirofiban, eptifibatide, enoxaparin, nadroparin, bivalirudin, fondaparinux and are limited regarding the different perioperative period due to increased risk of bleeding. Also other antihypertensive groups such as hypolipidemic including statins, beta-blockers, Angiotensin Converting Enzyme Inhibitors (ACEi), Angiotensin Receptor Blockers (ARBs).

The underutilization (lower than 50 %) of these drugs in postoperative discharge have shown an increased risk of myocardial infarction and death [16] [17].

Therefore the strategies for their standardised utilisation of these drugs in CABG are essential factors to reduce the risk of coronary diseases and improving the survival rate of the patients [18]. Use of antiaggregant in the early postoperative period have improved the life expectancy of coronary bypass and cardiovascular-related symptoms, reduced graft occlusion [19], while other anticoagulants such as warfarin are shown to play a role in patients with atrial fibrillation or with thromboembolism history [20]. Statins are used unless contraindicated in patients before and after operation [21].

Beta-Blockers utilisation is found more in postoperative atrial fibrillation prevention, hypertension [22], while ACEi is used more in myocardial infarction, left ventricular dysfunction, diabetes mellitus, chronic renal dysfunction. Also, calcium-blockers and diuretics are used for hypertension control.

Summarizing this number of patients affected by the cardiovascular disease in Kosovo is increasing and in particular, a considered number undergoing CABG exists. Moreover, pharmacotherapeutic evaluation is a necessary approach and intervention in perioperative procedures with the aim to reduce complications and increase the bypass patency and survival rate. Therefore, we aim to evaluate the drug utilisation rate in the perioperative state (before, after and after the visit) undergoing CABG and also identify targets for quality improvement with the preparation of guidelines and protocols for prudent use of drugs in cardiovascular surgery.

Material and Methods

This study is prospective observational study realised in 102 selected patients undergoing CABG in the period of hospitalisation in the Cardiovascular Surgery Clinic at the University Clinical Center of Kosovo (Prishtina, Kosovo) between the year 2016-2017.

The procedures in this study were conducted according to guidelines in the Declaration of Helsinki, and the study design was approved by Ethics Committee in Faculty of Medicine (Nr: 3625), University of Prishtina, Hasan Prishtina and University Clinical Center of Kosovo (Pristina, Kosovo).

Patients were selected from the randomly selected subset of the study cohort to assess medication and participation were voluntary. The sample size also fits calculation of sample size was performed using Raosoft software with a 5% margin of error, a 95% confidence level, and a 50% response distribution. Since the undergoing coronary artery bypass grafting patients in Kosovo was 120-150 in previous years. In this analysed year, total numbers in this period were 134 patients in this analysed year (according to the Hospital Statistics), which are in line sample size 102. Patients with a combination of operations, the absence to visit after the operation and those that did not survive the intervention after surgery were not included in our study.

Data were collected by the clinical pharmacologist, pharmacist and cardiac surgeon with properly designed form sheet. The drug use evaluation involved the therapy prescription and daily dosages in each patient, before the operation in the clinic, in the discharge after the operation and after the first visit in the clinic (≈ 2 months). The characteristics of patients such as age, gender, related comorbidities, metabolic and cardiovascular diseases, risk factors were collected.

The number of bypass arteries or veins and

priority of the intervention and available clinical indicated biochemical parameters in the period previous surgery such as Triglycerides, Cholesterol, Creatinine, AST, ALT, C-Reactive Protein (CRP), Left Ventricular Ejaculation Fraction (LVEF) were registered.

The general data's in the tables are expressed as prevalence or mean values. Drug use and daily dosages were calculated as (%) within each group.

Two sampled t-test were used for the comparison between the data between analysed groups regarding drug utilisation, whereas One-way ANOVA for comparison between the daily therapeutic dosages from each group or unpaired student t-test for differences between the two groups.

P value lower than 0.05 was considered statistically significant and represented the significant differences between the analysed groups. All analysis was performed using statistical software GraphPad PRISM (version 6.0).

Results

The study included data of 102 patients, aged 62.2 ± 10.3 with woman consulting 24% of the group analysed. The comorbidities in our study were Arterial Hypertension 67%, Angina Pectoris 42%, Type 2 Diabetes Mellitus 41%, Hypertriglyceridemia 21% and Hypercholesterolemia 18%. In our study, 36% were not smoking while 0-10 years smokers were 4%, 10-20 years 11%, 20-30 years 16% and 40-50 years 30%.

Table 1: Patient characteristics

Demographic and Clinical Patient Characteristics	
Gender (M/F)	78/24
Age	62.2 ± 10.3
Angina Pectoris	42 (%)
Hypercholesterolemia	18 (%)
Hypertriglyceridemia	28 (%)
Diabetes Mellitus	41 (%)
Hypertension	67 (%)
Smokers (before/now)	a) 0 years (36%) b) 1-10 years (4%) c) 10-20 years (11%) d) 20-30 years (16%) e) 30-40 years (30%)

Indication for angiography was included in all of our analyzed patients, and there was no previous CABG found, Cerebrovascular diseases (ischaemic disease, stroke and carotid stenosis) were widespread in 6 % of patients, whereas peripheral artery diseases (microvascular and macrovascular including varicose veins) 25%, left main coronary artery occlusion was present in 15%, and 17% of patients were with post-myocardial infarction status. Chronic renal failure was only 3% patients while 10% were with low degree renal insufficiency. Based on the priority of intervention, only 18% of patients were in urgency for cardiovascular surgery whereas 85% of patients were elective cases. Graft bypass results from the left internal mammary artery and SV. Demographics and clinical characteristics regarding cardiovascular disease, comorbidities, risk factors including smoking, type of intervention, the priority of intervention and type of graft data are featured in (Table 1 and 2).

Table 2: Patient characteristics regarding cardiovascular disorders and CABG intervention

Cardiovascular Characteristics of Patients in CABG	
Indication for coronary angiography	100 (%)
Previous CABG	0 (%)
Cerebrovascular disease	6 (%)
Peripheral artery disease	25 (%)
Left Main Coronary Artery Occlusion	15 (%)
Status post IM	17 (%)
Chronic Obstructive Pulmonary Disease	5 (%)
Chronic Renal Insufficiency/Renal Insufficiency	3/10 (%)
CABG type (CABG Isolated/Combination)	100/0 (%)
Intervention Priority (Urgency/Elective)	18/82 (%)
Arteries (LIMA) Vein (VSM) for CABG (5/4/3/2)	1/29/48/18 (%)

Biochemical parameters and cardiovascular data were within normal range values in all investigated patients as shown in the (Table 3), even though CRP values were in borderline, the specificity also exists for in individual values with higher AST and ALT values in 11% of patients, CRP higher values in 14% of patients, Creatinine in 10% of patients (data not shown).

Table 3: General biochemical - cardiovascular parameters of patients undergoing CABG

Biochemical/Cardiovascular Parameters	
Triglycerides (mmol/L)	1.83 ± 0.9
Cholesterol (mmol/L)	3.64 ± 1.1
Creatinine (µmol/L)	102.9 ± 15.8
AST (U/L)	28.2 ± 12.3
AST (U/L)	31.1 ± 14.5
CRP mg/dL	6.2 ± 4.8
Left Ventricular Ejaculation Fraction (%)	53.7 ± 10.9

The cardiovascular system drug utilisation rates in CABG patients in the period before the operation, after operation and visit after the operation are shown in the (Table 4).

Table 4: Cardiovascular pharmacological treatment administered in CABG Patients

Drug Utilization Rates in CABG Patients			
Type of Drugs	Before Operation (%)	After Operation (%)	Visit after Operation (%)
Beta Blockers	77.1	48.2	59.1
Calcium Blockers	4.9	9.6	8.1
ACEi	31.3	30.1	23.5
ARBs	22.9	3.6	8.5
Hydrochlorothiazide	25.2	1.6	15.6
Furosemide	15.7	97.6	52.8
Spironolactone	12.2	91.6	70.1
Nitrates	77.1	1.6	10.2
Xanthines	7.3	19.3	7.3
Statins	86.7	62.7	64.5
Amiodarone	1	21.8	8.8
Digitoxin	4.9	6.1	8.9

Moreover, the other drug utilisation administered for the treatment and management of CABG patients are shown in (Table 5).

Table 5: Other pharmacological treatment administered in CABG Patients

Type of Drugs	Drug Utilization Rates in CABG Patients Before Operation (%)	After Operation (%)	Visit after Operation (%)
Warfarin	0.5	4.8	0.5
Nadroparin	100	0.5	9.8
Clopidrogrel	0.5	33.8	21.9
Aspirin	0.5	97.6	76.5
IPP	49.4	65.1	51.8
H2 Blockers	37.4	35.5	38.5
Acetaminophen	4.8	35.5	12.2
76.5Indomethacin	0	14.5	7.3
Acetilcystine	2.4	72.3	11.8
Anxiolytics	6.5	4.9	4.9
Ceftriaxone	14.5	100	21.1
Insulins	32.5	42.2	27.9
Supplements	1	33.7	17.7

The daily dosage rates from the widely prescribed groups such as beta-blockers, ACEi, and ARBs, Diuretics are shown in (Figure 1-3).

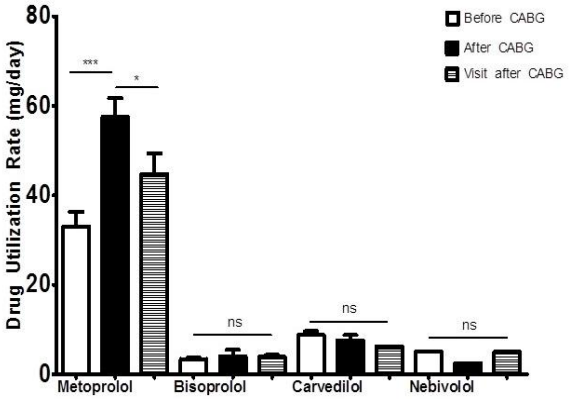

*Figure 1: Drug Utilization Rates expressed as daily dosage (mg/day) of beta blockers: Before CABG; After CABG and Visit after CABG. * P < 0.05, ** P < 0.01, *** P < 0.001*

In beta blockers only metoprolol dosages are increased after the operation (P<0.001), and de-creased in the visit after operation (P<0.05) (Figure 1).

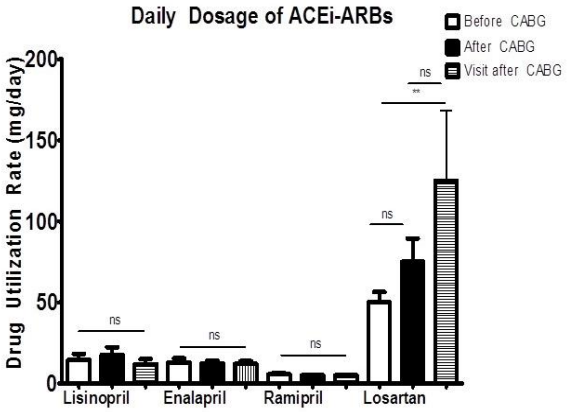

*Figure 2: Drug Utilization Rates expressed as daily dosage (mg/day) of ACEi/ARBs: Before CABG; After CABG and Visit after CABG. * P < 0.05, ** P < 0.01, *** P < 0.001*

From the ACEi or ARBs, only daily dosages of losartan were increased in the visit after the operation (P<0.01) (Figure 2), whereas in diuretics furosemide dosage was increased only in the period after the operation (P<0.05) (Figure 3).

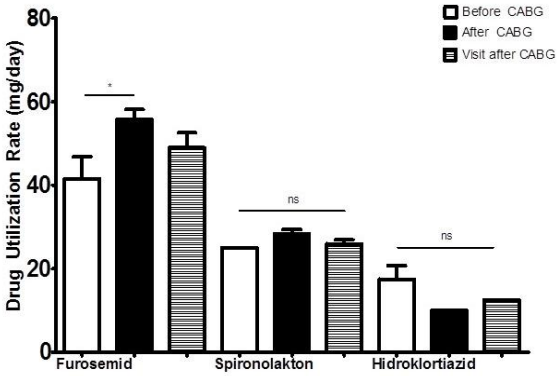

*Figure 3: Drug Utilization Rates expressed as daily dosage (mg/day) of Diuretics: Before CABG; After CABG and Visit after CABG. * P < 0.05, ** P < 0.01, *** P < 0.001*

The daily dosages regarding statins, antiacids (IPP and H2 Blockers), amiodarone are within the therapeutic values, but when compared from our analysed study groups they remain to be unchanged (P>0.05) (data not shown).

Discussion

In the present study, most of the patients were affected by cardiovascular diseases and comorbidities such as angina pectoris, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, hypertension and risk factors including smoking as observed in other studies [23].

Moreover, arterial diseases were also present including status post myocardial infarction, left main coronary artery occlusion, rare cases of cerebrovascular disease such as ischaemic stroke and carotid stenosis and renal failure and insufficiency. Elective patients have dominated, and SV was used more compared to a left internal mammary artery for the bypass grafting. Biochemical parameters previous intervention were within the normal ranges however there was a low number of patients which were presented with abnormal measured values. Left ventricular ejaculation fraction was standard in all analysed patients at a similar level to other reports [24] [25].

Pharmacotherapeutic evaluation has shown an increasing number of drugs in all groups corresponding three monitoring phases. The beta blockers were utilised with 77% before the operation, 48% after the operation and 59% visit after the operation. Metoprolol is the most prescribed medication with a higher dosage in the postoperative period. This data are in line with other previous findings [18]. Also, the higher utilisation in the

preoperative period was shown to improve clinical outcomes by reducing the number of complications and total mortality [26]. However, there are contradictory reports in beta blockers users which showed the no beneficial effect of beta-blockers in the clinical outcomes and mortality, even though the underutilization of beta blockers (30%) were lower when compared with our data [27]. Another study performed in the larger number of patients from the national database analysis in the including no emergent and without previous MI patients showed not to be favourable in the reduction of perioperative complications. However, the preoperative utilisation rates of beta-blockers were pretty similar to our findings [28].

Additional studies with the use of the beta blockers in the secondary prevention after CABG showed lower death and myocardial infarction rate and are found to be suboptimal with reduction rate from 89 after discharge and 77% after one year [17]. Also, the higher rates of utilisation of beta-blockers have been shown in other related studies (94%) [29] [30], which are not in agreement with our data.

In continuity ACEi drug utilisation rates were (31%, 30%, and 24%) and for ARBs (23%, 4%, and 9%), hydrochlorothiazide (23%, 2%, and 16%), which show a decreasing trend in postoperative and after the first visit. Only losartan daily dosage was increased in the visit after the operation. Our data are not by previous findings which showed increased utilisation rates of the ACEi/ARBs in postoperative CABG period, even though no effect were observed regarding death and re-hospitalisation for cardiovascular events [17] [30]. Also, the pre-operative utilisation of ACEi is shown to be higher compared to our data (30% vs 50%) which still did not reflect the in the improvement of clinical outcomes or adverse events (with the only increased risk of readmission for heart failure) [31]. Moreover, in another related study, the pre-operative utilisation of ACEi was 45 % with an increased number of the major adverse events (in particular renal dysfunction and atrial fibrillation) without an impact in mortality, stroke and myocardial infarction [32].

Diuretics such as furosemide and spironolactone utilisation were increased in the period after the operation, with slowly decreasing in the visit after operation (16%, 98%, and 53%) and (12%, 92%, and 70%). The daily dosage of furosemide was increased only after the operation. Also, the diuretic use was found to be in line with our data, and increased reports of major adverse events suggest their utilisation reduction before surgery (excluding to higher clinical evidence) [33].

Moreover antiaggregant drugs such as aspirin and clopidogrel were interrupted a week before operation in all patients, hence the utilization of them were continued after operation and in the visit after operation with (98% and 77%) for aspirin, (34 and 22%) for clopidogrel which underlies that the combination of dual antiplatelet therapy was not as reported studies [27], whereas the anticoagulant therapy with nadroparin has dominated only in the period before the operation. The daily dosages were similar in all groups.

Our data are by other findings in the antiaggregant drug utilisation in related studies by showing an increased utilisation in the postoperative operative period suggesting their preventive role and lower long-term cardiovascular events [17] [34].

Utilization of hypolipidemic drugs including statins were reduced after operation (87%, 63%, and 65%) however proportional daily dosages were found, which are in line with other recommendation which emphasises their continuity in the period after operation [35].

The increased utilisation rates of statins are recommended for the further improvement of cardiovascular clinical outcomes, perioperative and postoperative complications, inflammation [36]. Their postoperative use is also shown to be higher utilised and was associated with reducing recurrent ischaemic events and mortality [17] [29] [30], which were not by our findings due to their underutilization in the period after CABG. Moreover, according to the recent study, the loading dose of statins in the period after CABG is shown to be superior to regular dose regarding cardiovascular events and without proof of serious adverse events which might reflect their strategy in the dosing guidelines and prescribing in the future [21].

Based on our findings the utilisation of aspirin, beta-blockers, statins are comparable also with other related studies while ACEi/ARBs are underutilised in our study [18]. However, our findings are in line also in the utilisation of beta blockers, aspirin, ACE, higher in statin and underutilization nitrates [37]. In another study, the secondary prevention in patients undergoing coronary bypass, the utilisation of beta blockers, aspirin, a statin was in agreement with our findings, excluding the lower rate of ACEi or ARBs [38]. Other reports after operation have shown similar trends in beta blockers, statin, with lower ACEi/ARBs which also potentiate the necessity for the optimisation of the drug use in the postoperative period [39]. A possible explanation regarding lower rates of ACEi/ARBs utilisation may be the normal values of left ventricular ejaculation fraction, even though these values were not higher as previous studies [40].

Moreover, one retrospective study was observed by providing the recorded clinical data in the period when patients were admitted and also in the discharge. In this study, the use beta blockers, aspirin, and statin were in similar range but with higher ACEi, lower ARBs (only before the operation) compared to our findings. It is worth mentioning the fact that utilisation of beta blockers, ACEi, statins were

decreasing in the analysed years, and ARBs were increasing in the period before operation whereas after operation beta blockers and statins were decreasing [41].

The antiaggregants such as aspirin was regularly used and in a standard dosage and not all patients were combined with clopidogrel as dual antiplatelet.

Beta-blocker usage is in line with our data as recommended with previously reported guidelines for the pharmacotherapy after CABG [42]. However, ACEi or ARBs are not used properly in all patients due to normal LVEF in our study. Moreover, aldosterone antagonists need to be reevaluated due to their limited use in LVEF < 35% or cardiac insufficiency II-IV patients. Statin utilisation was not monitored properly and titrated in our study.

Approximate data regarding existing protocol and evidence for the management of patients after CABG are also found in other guidelines from American heart association which also relies on the type of evidence and relevant treatment [8].

Other utilised drugs in our study were: vasodilators including nitrates with (77%, 2% and 10%) and xanthines with (7%, 19% and 7%). Even though amiodarone utilisation were (1%, 18%, 7%) more should be done to replace it with beta blockers and also the use of statins with the magnesium in the same period [39]. Also, the use of amiodarone in the prevention of atrial fibrillation only 24 hours after operation intravenously and in lower dosages is another promising strategy [43].

Cardiovascular pharmacotherapeutic approaches in diabetes mellitus consisted usage of insulin which was accompanied with a reduction in the period after the operation, probably due to the increased risk of clinical features in patients with CABG [44].

Also, the antiacids such as IPP or H2 blockers are mainly used as prophylaxis regarding the surgical intervention which is a common indication [45] and decreases in the visit after the operation. Other drugs such as analgesics including acetaminophen are indicated as needed mostly in postoperative period with nonsteroidal anti-inflammatory drugs indomethacin, acetylcysteine dominated in the period after the operation and reduced in the visit after operation with also cephalosporin antibiotics. The frequency of NSAID administration after CABG has declined since the FDA recommendations and advice due to safety concerns and from 2004 (39%) to 2010 (29%) which may also impact the lower utilization in our group of patients (15%) [46], also the higher utilization of acetylcysteine need to be also considered to its scientific evidence in the prevention of atrial fibrillation to undergoing CABG patients [47].

Rare cases of digoxin, trimetazidine, tamsulosin, doxazosin, levotiroksin, fluoxetine, metformin, and ipratropium-budesonide were also founded.

In the meantime with our study regarding utilisation and daily dosages, we have also performed experimental studies for the alternative in compounds (arctigenin) for vasorelaxation and decreasing inflammation level in SV tissues [23].

In addition to this omega 3 polyunsaturated fatty acids were shown to be beneficial in inflammation and contractility in SV tissues [48].

There are undergoing similar approaches by other groups by investigating endothelin-1 antagonists [49], levosimendan [50], anti-ischaemic agents including ranolazine were shown to improve postoperative fibrillation in patients after CABG [40], and additional pharmacologic agents which inhibit the vasospasm of coronary grafts [51].

The drug utilisation after CABG have shown to be an important factor regarding long-term management of the clinical outcomes, the adherence of this drugs were not satisfactory after the first year after the revascularisation period [29], which suggests different strategies and interventions increase the improvements of clinical outcomes and bypass patency rates.

Despite the clinical relevance of this study, the absence of official protocols which are in the procedure of establishment to maintain effective use of drugs may affect drug prescription and utilization, long-term monitoring (more than three months) after CABG, short period of study (for 1-5 years after CABG) and the adherence monitoring after discharge including also clinical outcomes and adverse events could be considered as a limitations of our study. Taking this into consideration our work may set the stage for larger investigational studies aimed at evaluating the utilisation and also drug adherence, long-term monitoring including also the long period after the discharge and clinical outcomes and adverse events.

In summary in our study, we have found that therapeutic groups such as beta blockers, statins, aspirin, thiazides, nitrates (before the operation), furosemide and spironolactone are the most utilised drugs. However, we found low utilisation rate for ACEi, ARBs, clopidogrel, nadroparin, warfarin, xanthines, amiodarone, calcium blockers. Daily dosages were different compared to before CABG only in metoprolol, losartan, and furosemide.

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Clinical Science

The Outcome of Using a Jamshidi Biopsy Trocar Needle in a Novel Technique for Bone Grafting in Percutaneous Internal Fixation of Scaphoid Non-Union

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Abstract

INTRODUCTION: We report the outcome of using a novel technique of minimally invasive internal fixation and distal radius bone grafting using the Jamishidi Trephine needle and biopsy/graft capture device.

METHODS: The technique utilises a 8 mm incision at the distal pole of the scaphoid. The non-union is excavated using the standard Acutrak drill. An 8 gauge Jamshidi trephine needle is used to harvest bone graft from the distal radius which is impacted into the scaphoid and fixed with an Acutrak screw. Fifteen patients were available for retrospective review, 14 male, age mean 29.5 (15-56). Average time from injury to surgery was 167 days (45-72). Fractures classified according to Herbert giving 7 D1 and 8 D2 fractures, 14 waist and 1 proximal pole fractures, all of which had no humpback deformity.

RESULTS: Sixty-six percentages of the fractures went onto unite, 4/7 D1 and 6/8 D2 united ($p > 0.05$). Seventy-five percentages of fracture that had surgery in less than 3 months from time of injury went onto unite, whereas only 63% united in patients who had surgery later than 3 months ($p > 0.05$). DASH outcome for all patients improved from 86 down to 32 ($p < 0.05$). With those that united going down from 90 to 6. Those that did not unite went from 81 to 61.

CONCLUSION: The Jamshidi bone grafting technique shows comparable results (union rate 66%) to other techniques published in the literature (27-100%) providing the surgeon with an alternative and less demanding procedure than open scaphoid non-union surgery.

Introduction

The management of scaphoid non - union, continues to be a wide scale problem due to the varying union rates achieved with vascularised and non - vascularised bone grafting. Due to the non-reproducible results outside of specialist centres, vascularised bone graft still has not fully been embraced.

We analysed our results of a novel technique of non - vascularised bone grafting using a Jamshidi biopsy trocar needle in non - unions that had not fallen into a humpback malunion.

Methods

Between 2009 and 2014, 50 patients with scaphoid fractures who underwent an operative procedure at a busy District General Hospital were identified by computer data capture software (Bluespier, Droitwich, UK). Forty-five patients with an acute fracture, humpback malunion deformity, avascular necrosis, proximal pole fracture or incorrect coding were excluded. This left 15 cases that underwent percutaneous bone grafting and Acutrak screw fixation for our study. There were no formalised inclusion criteria, but we found that after a minimum period of immobilisation of 6 weeks and no definite signs of bony union an informed discussion were undertaken with the patient regarding the risks and

benefits of performing surgery. Most patients who consented to surgery were young, self - employed males. Four shot - scaphoid radiographs were taken preoperatively and then classified according to the Filan and Herbert classification into either D1 - fibrous union or D2 - pseudoarthrosis.

Figure 1: Eight mm incision at distal pole of scaphoid

Initial treatment involved a below elbow plaster or splint immobilisation of at least 6 weeks. Patients who failed to show progression towards union after an initial period of non - operative treatment were then considered for a further conservative measure or operative treatment. In conjunction with patient consultation, a decision was then made to proceed with operative intervention with our described technique. Patients were followed up using clinical and radiological examination either with radiographs or 3 - dimensional reconstruction such as CT or MRI. After surgery, the patient was immobilised in plaster for 6 weeks. At 6 weeks they were followed up with scaphoid series radiographs and clinical examinations while being allowed to mobilise.

Figure 2: Eight mm incision over listers tubercle

Union was confirmed with clinical and radiological examinations, and patients were asked to complete the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire. Outcomes used for analysis were union rate, time from injury to surgery, the effect of Herbert classification and its effect on union and DASH scores. We defined early surgery from the time of injury as surgery performed within 120 days of the injury, and hence late surgery after 120 days.

Outcomes were assessed as time to radiological union, or salvage procedure of excision distal pole and using preoperative and postoperative DASH score.

Figure 3: Jamshidi needle and tracer set

We used XLSTAT (Addinsoft, USA) for all statistical tests. Non-parametric tests were used for our results. The chi-squared test was used for categorical variables, and the Wilcoxon Rank test was used for continuous variables.

Figure 4: Harvesting of distal radius bone graft under fluoroscopic guidance

The procedure is carried out on a radiolucent arm table with upper arm tourniquet control. Two small incisions are utilised. Fluoroscopy is used to identify the distal pole of the scaphoid and an 8 mm volar incision is made in the line of the scaphoid at the distal pole (Figure 1).

Dissection is continued down to the distal pole and wire is drilled down the scaphoid so that it is located in central position on the AP, Lateral and oblique views. The screw length is measured, and then the scaphoid is drilled using the ‘Standard’

Acutrak drill bit. The authors prefer to carry out all drilling on hand power which allows for much more controlled scaphoid excavation. A dorsal incision of 5mm based just proximal to Lister's tubercle is made, and a bare area of bone is identified (Figure 2).

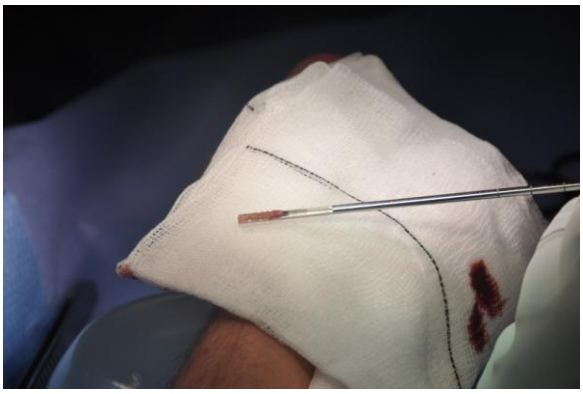

Figure 5: Distal radius bone graft harvest

An 8 Gauge Jamshidi trocar and biopsy needle (Figure 3) is then inserted into the distal radial metaphysis (Figure 4) in a corkscrew motion to capture a column of cancellous tube-shaped autograft (Figure 5).

The capture device fits exactly into the drill hole made by the standard Acutrak drill bit (Figure 6).

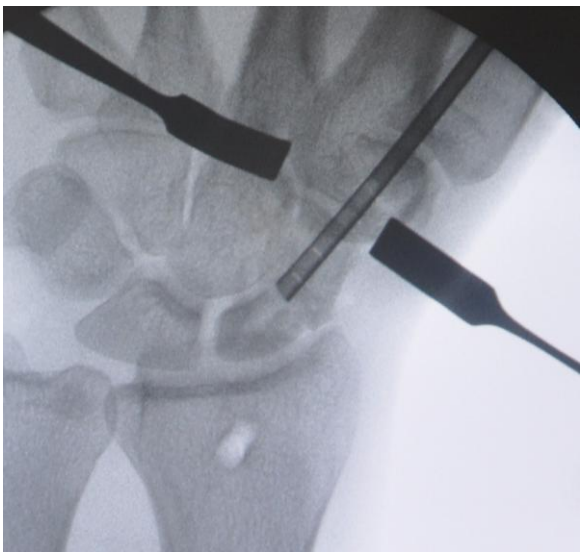

Figure 6: Insertion of tracer into scaphoid Insertion of tracer into scaphoid

The hook-shaped biopsy extractor is then used to expel and impact the cancellous autograft into the scaphoid non - union (Figure 7).

Multiple grafts can be extracted and impacted into scaphoid until it becomes difficult to insert anymore. The guide wire is then re-drilled under fluoroscopy control into the centre -centre position. The screw length does not have to be re-measured as there is no change in the shape of the scaphoid with the introduction of the graft.

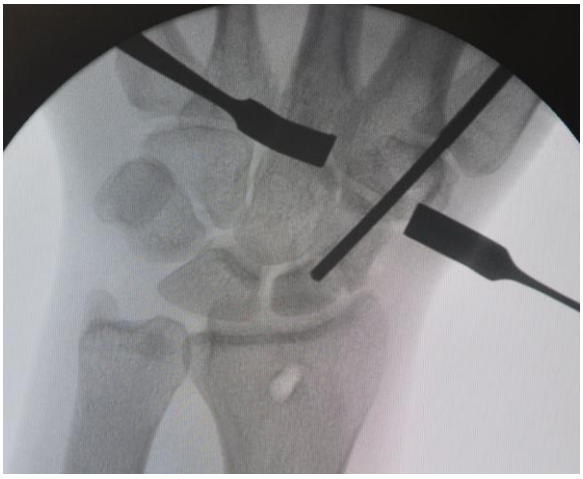

Figure 7: Graft packed into scaphoid using pusher

The drill bit is then passed over the guide wire but in reverse to impact the graft swarf into the scaphoid bone and also make room for the screw. The screw is then inserted, and radiographs were taken to ensure correct positioning (Figure 8).

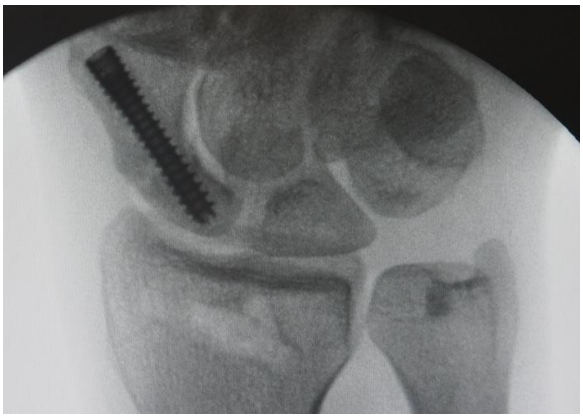

Figure 8: Acutrak screw to compress scaphoid

Results

In the 14 men and 1 woman, the average time from injury to the time of surgery was 167 days (Range 45 - 472). Mean age of 29.5 years (range 15 - 56). All patients were studying, in employment or actively seeking employment. Two wrist surgeons reviewed the pre-operative radiographs, and any discordance agreed upon after discussion. This classification review resulted in seven D1 (fibrous union) and eight D2 (pseudoarthroses) fractures. Fourteen fractures were of the scaphoid waist and only one proximal pole.

The average time to union was 70.9 days (range 41 - 293). One patient was an outlier at 293 days, and if this patient is excluded, then the average reduces to 46.2 days (range 41 - 58 days).

Ten out of 15 patients went onto unite of which 4 of these were D1 fibrous unions, and 6 were D2 pseudoarthroses. Hence 4 out of 7 D1 fractures united and 6 out of 8 D2 fractures united. Despite D2 having a higher union rate, there is no significant difference between the 2 Herbert groups ($p > 0.05$).

Of the 5 that did not unite the average time from injury to surgery was 138 days (range 55 - 208). This is compared to 180 days for the ten that united (range 45 - 472). The patient with the proximal pole fracture did not unite but was pain-free, with good function.

Comparing the two groups of those having to wait less than 120 days compared to more than 120 days gave a 75% vs 63% union rate, this resulted in no statistical difference between the 2 groups when examining time from injury to surgery and its effect on bony union ($p > 0.05$).

DASH outcomes improved from a mean preoperative score of 86 (68-94) to 32 (0-100) for all patients which were statistically significant ($p < 0.05$). Those patients that united improved from 90 down to 6 whereas those that did not unite went from 81 to 61. The magnitude of improvement following surgery between those that did and those that did not unite was statistically significant ($p = 0.02$).

There is no difference in DASH scores in those who had surgery before 120 days verses those after 120 days ($P= 0.686$).

Table 1: Outcomes of Surgery

Patient	Age	Herbert classfn	Proximal pole or Waist	Outcome	Time to union	Time from injury to surgery	Pre-op DASH	Post op DASH
JB	15	D2	Waist	United	44	274	84	0
SW	22	D1	Waist	United	48	472	87	18
DS	19	D1	Waist	United	293	182	93	15
CD	49	D2	Waist	United	51	76	91	0
CJ	30	D2	Waist	United	41	236	88	0
LM	21	D2	Waist	United	41	93	86	18
MW	20	D2	Waist	United	58	157	93	0
PW	40	D1	Waist	United	42	45	94	0
DT	32	D2	Waist	United	49	86	89	6
DS	34	D1	Waist	United	42	187	88	0
AF	26	D2	Waist	Non-united	N/a	175	88	84
PR	23	D1	Waist	Non-united	N/a	128	68	27
GD	24	D2	Waist	Non-united	N/a	208	91	76
SS	25	D1	Waist	Non-united	N/a	55	94	94
PA	34	D1	Proximal Pole	Non-united	N/a	124	68	21

Discussion

The management of scaphoid non-union continues to be a problem for surgeons who deal with scaphoid fractures. The goals of treatment for scaphoid non-union include union, correction of deformity, and relief of symptoms and limitation of arthrosis [7]. Factors that adversely affect the outcome of scaphoid non - union included the duration of non - union, no punctate bleeding of the proximal pole at the time of surgery and failed previous surgery [11]. Our study involved percutaneous surgery hence we could not identify whether there was punctate bleeding from the proximal pole and none of the patients had undergone previous surgery.

Minimally invasive surgery is indicated in early scaphoid without cystic bone resorption, without appreciable collapse of the scaphoid architecture and avascular necrosis of the proximal pole [2].

Non-vascularised bone graft has varying success in the literature with union rates of 66% iliac crest vs 67% distal radius with donor site pain in the iliac crest group [11]. In a different study of 5246 cases of non-union, the group which was fixed with non-vascularised bone graft showed a union rate of 84%(6). Other groups have found 100% union rates with iliac crest bone graft [1]. Our study shows a rate of 66% which is comparative with the results from Tambe's group [11] but inferior to the other groups.

Comparing bone grafting techniques versus non-bone grafting techniques the authors are aware that there is literature supporting percutaneous fixation without grafting. Union rates are similar to ours published. However, we feel that in our experience the minimal extra surgical time provides a bone graft which speeds up a time to union. Union rates have been reported in non-bone grafting papers as averaging thirteen [5], fourteen [8] and nineteen [9] weeks. In our study the average was ten weeks and when the one outlier is excluded this reduced to six weeks. Hence we feel the advantage of our technique is the speed at which the bone unites compared to non-bone grafting techniques. This is especially important in the population that is being treated, those of young, fit, active males in current employment looking to get back to work as soon as possible.

Vascularised bone grafting techniques seem to achieve superior rates of the union in specialist centres however when these are attempted elsewhere lower rates of the union are attained. Union rates vary from 27% to 100% [9] [10] [12]. Pedicles are usually harvested from the distal radius. However, more advanced techniques such as medial femoral condyle vascularised graft are producing [4] high rates of the union. Taking these superior results from specialist centres into account the jury is still out on whether there is truly an advantage for vascularised against non-vascularised bone graft. In a rare randomised control trial comparing vascularised to non-vascularised grafts, there was no difference between the two groups in union rates, time to union and functional results [1].

We feel that this is a technique which is not technically demanding, reproducible in any centre and has minimal if any donor site morbidity. We are aware that the general outline of the technique has previously been described, but we feel the novelty lies in 1) the use of a Jamshidi needle, 2) the perfect fit of the Jamshidi harvesting tool into the drill hole created

by the Acutrak drill and 3) the ability to use the graft extractor to impact the graft into the non - union site.

We acknowledge limitations in our study being the absence of dynamometry and grip strength testing and also that it is an underpowered study as exhibited by lack of any statistical differences. Interestingly with our technique, there was no significant difference between union rate of surgery before versus those after 120 days, but this is limited by the small numbers of patients in the study.

Our practice has changed after analysing our results, and we are ensuring that patients who are showing any progression towards a delayed union receive early operative intervention and we are only using this technique on waist fractures. If patients present with a marked delay we are now considering iliac crest bone grafting due to the shown increase in union rates in Braga-Silva's group [1].

Our union rate is 66% overall which is comparable to rates across the literature and also results in satisfactory subjective patient outcomes as measured by DASH scores.

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Metabolic Profiles in Obese Children and Adolescents with Insulin Resistance

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Abstract

BACKGROUND: In the past several decades, the increasing frequency of overweight and obese children and adolescents in the world has become a public health problem. It has contributed significantly to the already high tide of diabetes, cardiovascular and cerebrovascular diseases.

AIM: To investigate the frequency of insulin resistance and to evaluate the metabolic profile of insulin resistant and non-insulin resistant obese children and adolescents.

SUBJECTS AND METHODS: The study included 96 (45 boys, 51 girls) obese children and adolescents aged 4-17 years old (10.50 ± 2.87 years). Only participants with Body Mass Index ≥ 95 percentile were included. We analysed sera for fasting insulin levels (FI), fasting serum triglycerides (TG), total serum cholesterol (TC), fasting plasma glucose (FPG) and plasma glucose 2 hours after the performance of the oral glucose tolerance test (2-h G). Homeostatic model assessment for insulin resistance (HOMA-IR) index was calculated as fasting insulin concentration (microunits per millilitre) x fasting glucose concentration (millimolar)/22.5. The value of HOMA-IR above 3.16 was used as a cut-off value for both genders.

RESULTS: Insulin resistance was determined in 58.33% of study participants. Insulin resistant participants had significantly higher level of 2-h G ($p = 0.02$), FI level ($p = 0.000$) as well as TG levels ($p = 0.01$), compared to non-insulin resistant group. Strikingly, 70.73% of the pubertal adolescents were insulin resistant in comparison to 49.09% of the preadolescents ($p = 0.03$). Significantly higher percentage of insulin-resistant participants were girls ($p = 0.009$). Moreover, a higher percentage of the girls (70.59%) than boys (44.44%) had HOMA-IR above 3.16 and had elevated FI levels (70.59% vs 48.89%). The difference in the frequency of insulin resistance among obese versus severely obese children and adolescents was not significant ($p = 0.73$, $p > 0.05$). Our study results also showed positive, but weak, correlation of HOMA-IR with age, FPG, TG and BMI of the participants ($p < 0.05$).

CONCLUSION: Higher percentage of insulin-resistant participants was of female gender and was adolescents. In general, insulin resistant obese children and adolescents tend to have a worse metabolic profile in comparison to individuals without insulin resistance. It is of note that the highest insulin resistance was also linked with the highest concentrations of triglycerides.

Introduction

Obesity is a chronic medical condition where increased adipose tissue growth impairs metabolic health, increases the risk for type 2 diabetes mellitus, cardiovascular diseases, dyslipidemia, hypertension and insulin resistance [1] [2] [3] [4] [5].

Obesity rates are constantly rising globally, in line with growing prevalence of obesity and overweight in pediatric patients. This prevalence has risen by 47.1% between 1980 and 2013 [6]. One in 3 children in the US is overweight or obese [7]. In Europe, the highest rates of obese children are observed in the south-eastern European countries [8]. Also, the rise in obesity is occurring in earlier ages [9] [10]. It is of note there has been plateauing in the prevalence of obesity in developed countries [11].

Insulin resistance is a key component of the metabolic syndrome [12]. Childhood insulin resistance could impair metabolic health and is associated with metabolic syndrome, prediabetes, type 2 diabetes

mellitus and several other cardiometabolic risk factors [13][5]. One of the earliest complications, as a consequence of insulin resistance in childhood obesity, is the impairment of glucose metabolism [14]. However, it should be mentioned that insulin resistance may not always be present in obese individuals [13].

There are several methods that could be used for assessing insulin resistance: hyperinsulinemic euglycemic clamp and intravenous glucose tolerance test, homeostasis model assessment (HOMA), quantitative insulin sensitivity check index (QUICKI), McAuley index, Matsuda index, Belfioreindex, Cederholm index, Avignonindex, Stumvollindex. Although hyperinsulinaemic-euglycaemic clamp test is the gold-standard for the measurement of insulin sensitivity, homeostatic model assessment has been considered as a useful, cost-effective, and most widely used tool for the assessment of insulin resistance [15] [16]. The interaction between HOMA-IR and BMI in preadolescence predicts the likelihood of having metabolic syndrome in late adolescence. Therefore reducing insulin resistance in children at the age of 9-10 years could lead to metabolic syndrome prevention at the age of 18-19 years [17]. Moreover, both metabolic syndrome and type 2 diabetes mellitus in adulthood could be predicted form the existence of pediatric metabolic syndrome [18]. Impaired fasting glucose, type 2 diabetes mellitus in early adulthood could also be predicted using the HOMA-IR index for insulin resistance in the preadolescent age [19]. However, it is the HOMA-IR threshold levels for defining insulin resistance have been varying greatly hampering the interpretation of the results [20].

Our study aimed to investigate the frequency of insulin resistance and to evaluate the metabolic profile of insulin resistant and non-insulin resistant obese children and adolescents.

Methods

This cross-sectional study included a total of 96 obese children and adolescents referred to the University Clinic of Child Diseases – Skopje between 2009 and 2017 for investigation and treatment for obesity. The cohort included 45 boys and 51 girls aged 4-17 years (10.50 ± 2.87). Study participants were classified as preadolescents if they were between 4 and 11 years old and adolescents if they were between 12 and 18 years old [21]. Obesity was the only inclusion criteria, as defined from the sex- and age-specific growth charts provided by the Centers of Disease Control and Prevention (CDC) – Body Mass Index ≥ 95th percentile [22]. As severely obese participants were classified those whose BMI was 120% of the 95th percentile for age and sex [23]. Study participants with secondary obesity syndromes, syndromal obesity, primary hyperinsulinemia, hypothyroidism, long-term corticosteroid use, primary hyperlipidemia, diabetes mellitus type 1, or other weight affecting disorders as well as chronic, hereditary, endocrine, infectious and inflammatory disorders were excluded. This study was approved by the Ethical Committee of the Faculty of Medicine of the University “Ss. Cyril and Methodius” – Skopje, Macedonia and was carried out by the Declaration of Helsinki.

Participants’ height (to the nearest millimetre) and weight (to the nearest decimal fraction of kg) were measured according to the standard procedures while participants’ were barefoot and dressed only in light underwear. Body Mass Index was calculated as weight in kilograms divided by height in square meters. An oral glucose tolerance test was performed with a dose of 1.75 g glucose/kg body weight (up to a maximum of 75 grams) by the World Health Organization (WHO) recommendations [24]. Blood samples were collected in at 0 minutes and in several intervals, at 30, 60, 90, 120, 150, 240 minutes, after the glucose load. All study participants fasted for 12 hours after which venous sampling was done. The levels of plasma glucose, serum triglycerides, and total serum cholesterol were determined using clinical chemistry analyser ARCHITECT c4000 (Abbott Diagnostics). Insulin levels were measured in an analyser IMMULITE® 2000 immunoassay system (SimensHealthcareDiagnostics). Homeostatic model assessment for insulin resistance (HOMA-IR) index was calculated: fasting insulin concentration (microunits per millilitre) x fasting glucose concentration (millimolar)/22.5 [25].

Serum fasting triglyceride levels ≥ 100 (mg/dL) for children aged 0-9 years and > 130 for children aged 10-19 years old defined the abnormally elevated level of serum triglycerides. Total serum cholesterol ≥ 200 mg/dL was considered abnormal [26]. To convert mg/dL to mmol/L values of total cholesterol and triglycerides were multiplied by 0.0259 and 0.0113, respectively;

Impaired fasting glucose was defined if the fasting plasma glucose level was ≥ 5.6 but < 7 mmol/L, impaired glucose tolerance if two-hours of plasma glucose after OGTT performance was ≥ 7.8 but < 11.1 mmol/L. Type 2 diabetes mellitus was defined if the fasting plasma glucose level was ≥ 7 mmol/L, or two -hours of plasma glucose after OGTT performance was ≥ 11.1 mmol/L [27]. Fasting insulin levels ≥ 15 mU/ml were considered hyperinsulinemic levels [28]. Insulin resistance was defined as HOMA-IR index > 3.16 [29].

Continuous data were expressed as mean ± SE. Categorical data were expressed as frequencies and percentages. All continuous variables were first tested for distribution normality using Smirnov - Kolmogorov and Shapiro-Wilk normality tests. Depending on the normality of the distribution

parametric and non-parametric statistical tests were conducted. For the analysis of normally distributed data t-test was performed and Pearson correlation coefficients were calculated. In cases where data were not normally distributed Man Whitney U test was conducted, and Spearman correlation coefficients were calculated. The Pearson Chi-square was used to analyse differences in categorical variables. Data were analyzed by using statistical package STATISTICA 8.0. P values < 0.05 were considered statistically significant.

Results

Our study comprised of 96 obese children and adolescents (45 boys and 51 girls), aged between 4 - 17 years (Table 1). Girls had significantly higher BMI, fasting insulin levels and HOMA-IR compared to boys ($p < 0.005$). Other metabolic parameters (fasting plasma glucose, plasma glucose 2 hours post the glucose load after the OGTT, total cholesterol and triglyceride level) did not differ significantly between genders (Table 1).

Table 1: Clinical and metabolic characteristics of obese children and adolescents according to gender

		All	Boys		Girls		
Variable	Participants No.	% or mean ± SE	Participants No.	% or mean ± SE	Participants No.	% or mean ± SE	*p*-value
Degree of obesity*	96	-	45	-	51	-	0.45[1]
Obese	27	28.13	11	24.44	16	31.37	
Severely obese	69	71.88	34	75.56	35	68.63	
Preadolescents vs. adolescents*	96	-	45	-	51	-	0.03[2]
Preadolescents	55	57.29	31	68.89	24	47.06	
Adolescents	41	42.71	14	31.11	27	52.94	
Age (years)††	96	10.50 ± 0.29	45	10.17 ± 0.40	51	10.79 ± 0.42	0.18
Wieght (kg)††	96	74.97 ± 2.39	45	72.86 ± 3.73	51	76.84 ± 3.08	0.18
Height (cm)††	96	150.52 ± 1.63	45	149.20 ±2.68	51	151.69 ± 2.03	0.45
BMI (kg/m^2)††	96	31.68 ± 0.49	45	30.63 ± 0.58	51	32.62 ± 0.74	0.03
FPG (mmol/L)†	96	4.18 ± 0.04	45	4.16 ± 0.07	51	4.20 ± 0.06	0.65
2-h G (mmol/L)†	93	5.67 ± 0.12	45	5.70 ± 0.18	48	5.64 ± 0.16	0.79
FI (uU/mL)††	96	20.35 ± 1.09	45	16.93 ± 1.46	51	23.37 ± 1.47	0.000
HOMA-IR††	96	3.80 ± 0.21	45	3.14 ± 0.29	51	4.37 ± 0.29	0.000
TC (mmol/L)†	88	4.05 ± 0.08	41	4.04 ± 0.12	47	4.06 ± 0.10	0.89
TG (mmol/L)††	88	1.20 ± 0.06	41	1.11 ± 0.09	47	1.27 ± 0.07	0.07

*Obtained from χ^2 test for comparison of categorical variables; †Group comparison was examined using Mann-Whitney U test for continuous data;††Group comparison was examined using t test for continuous data; [1]Pearson $\chi^2 = 0.57$, df=1; [2]Pearson $\chi^2 = 4.66$, df=1; BMI, Body Mass Index; FPG, fasting plasma glucose; 2-h G, plasma glucose two hours post the glucose load during the oral glucose tolerance test; FI, fasting insulin level; HOMA-IR, homeostatic model assessment of insulin resistance; TC, total cholesterol; TG, triglycerides.

The second table shows characteristics of insulin resistant and non-insulin resistant obese children and adolescents. Adolescents had a statistically significant higher frequency of insulin resistance ($p = 0.03$). Also, the significantly higher percentage of participants with insulin resistance were girls compared to boys (64.29% vs 35.71%, $p = 0.009$). The mean age, as well as BMI, was significantly higher in the insulin-resistant group ($p < 0.05$). Study participants who had insulin resistance had significantly higher values of some of the metabolic parameters (plasma glucose 2 hours post the glucose load after the OGTT, fasting insulin, level of triglycerides) compared to participants in the non-resistant group. The values of fasting plasma glucose and total serum cholesterol showed no statistically significant difference between the two tested groups.

Table 2: Clinical and metabolic characteristics of obese children and adolescents according to insulin resistance

		Non-insulin resistant (non-IR)		Insulin resistant (IR)		
Variable	Participants No.	Participants No.	% or mean ± SE	Participants No.	% or mean ± SE	*p*-value
Degree of obesity*	96	40	-	56	-	0.73[1]
Obese	27	12	30.00	15	26.79	
Severely obese	69	28	70.00	41	73.21	
Preadolescents vs. adolescents*	96	40	-	56	-	0.03[2]
Preadolescents	55	28	70.00	27	48.21	
Adolescents	42	12	30.00	29	51.79	
Gender						0.009[3]
Boys	45	25	62.5	20	35.71	
Girls	51	15	37.5	36	64.29	
Age (years)††	96	40	9.79 ± 0.50	56	11.00 ± 0.34	0.04
Wieght (kg)††	96	40	67.05 ± 3.21	56	80.63 ± 3.21	0.005
Height (cm)††	96	40	146.76 ± 2.64	56	153.21 ± 2.02	0.03
BMI (kg/m^2)††	96	40	30.35 ± 0.63	56	32.64 ± 0.68	0.02
FPG (mmol/L)†	96	40	4.09 ± 0.07	56	4.25 ± 0.06	0.07
2-h G (mmol/L)†	93	39	5.35 ± 0.19	54	5.89 ± 0.15	0.02
FI (uU/mL)††	96	40	11.81 ± 0.59	56	26.45 ± 1.30	0.000
TC (mmol/L)†	88	35	3.88 ± 0.11	53	4.15 ± 0.10	0.08
TG (mmol/L)††	88	35	0.99 ± 0.07	53	1.33 ± 0.08	0.005

*Obtained from $\chi 2$ test for comparison of categorical variables; †Group comparison was examined using Mann-Whitney U test for continuous data;††Group comparison was examined using t-test for continuous data; [1]Pearson $\chi^2 = 0.12$, df=1; [2]Pearson $\chi^2 = 4.53$, df=1; [3]Pearson $\chi^2 = 6.72$, df=1; BMI, Body Mass Index; FPG, fasting plasma glucose; 2-h G, plasma glucose two hours post the glucose load during the oral glucose tolerance test; FI, fasting insulin level; TC, total cholesterol; TG, triglycerides.

On Table 3 are demonstrated percentages of abnormal metabolic parameters among study participants by gender and insulin resistance status according to HOMA-IR. The frequency of elevated fasting insulin levels was significantly higher in girls ($p = 0.03$). The distribution of other metabolic parameters between boys and girls did not reveal any statistical significance. The percentage of abnormal level of fasting insulin was significantly higher in obese insulin-resistant children and adolescents. Also, the elevated triglycerides level was more prevalent in the insulin-resistant group. However, the differences in the distribution of other abnormal laboratory parameters among study participants showed no statistical significance.

Table 3: Frequency (%) of abnormal laboratory parameters among study participants

Variable	Participants No.	All n (%)	Gender: Boys Participants No.	Boys n (%)	Gender: Girls Participants No.	Girls n (%)	p-value*	HOMA-IR: Non-insulin resistant (non-IR) Participants No.	Non-insulin resistant (non-IR) n (%)	HOMA-IR: Insulin resistant (IR) Participants No.	Insulin resistant (IR) n (%)	p-value*
FPG (mmol/L)	96	1 (1.04)	45	1 (2.22)	51	0 (0.00)	0.28[1]	40	0 (0.00)	56	1 (1.79)	0.40[7]
2-h G (mmol/L)	93	3 (3.23)	45	1 (2.22)	48	2 (4.17)	0.60[2]	39	2 (5.13)	54	1 (1.85)	0.38[8]
FI (uU/ml)	96	58 (60.42)	45	22 (48.89)	51	36 (70.59)	0.03[3]	40	5 (12.5)	56	53 (96.64)	0.000[9]
TC (mmol/L)	88	5 (5.68)	41	3 (7.32)	47	2 (4.26)	0.75[4]	35	2 (5.71)	53	3 (5.66)	0.27[10]
TG (mmol/L)	88	30 (34.09)	41	13 (31.71)	47	17 (36.17)	0.10[5]	35	9 (25.71)	53	21 (39.62)	0.01[11]
HOMA-IR	96	56 (58.33)	45	20 (44.44)	51	36 (70.59)	0.009[6]	-	-	-	-	-

*Obtained from χ^2 test for comparison of categorical variables; [1]Pearson $\chi^2 = 1.15$, df=1; [2]Pearson $\chi^2 = 0.28$, df=1; [3]Pearson $\chi^2 = 4.71$, df=1; [4]Pearson $\chi^2 = 0.57$, df=2; [5]Pearson $\chi^2 = 4.57$, df=2; [6]Pearson $\chi^2 = 6.72$, df=1; [7]Pearson $\chi^2 = 0.72$, df=1; [8]Pearson $\chi^2 = 0.78$, df=1; [9]Pearson $\chi^2 = 65.83$, df=1; [10]Pearson $\chi^2 = 2.60$, df=2; [11]Pearson $\chi^2 = 8.75$, df=2; FPG, fasting plasma glucose; 2-h G, plasma glucose two hours post the glucose load during the oral glucose tolerance test; FI, fasting insulin level; TC, total cholesterol; TG, triglycerides; HOMA-IR, homeostatic model assessment of insulin resistance.

On Figure 1 the differences and the frequency of abnormal metabolic parameters between participants in two age groups (preadolescents: 4-12; adolescents: ≥ 12-18 years) are presented. There was a higher percentage of plasma glucose 2 hours post the glucose load after the OGTT, elevated fasting insulin and HOMA-IR among adolescents in comparison to preadolescents. All adolescents have undergone puberty, in contrast to only 15% of the preadolescents.

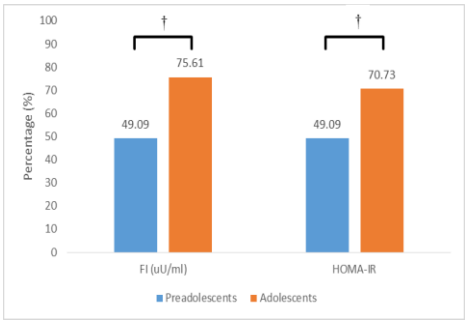

Figure 1: Distribution of abnormal parameters among study participants according to age group. FI, fasting insulin level; HOMA-IR, homeostatic model assessment for insulin resistance. †p value < 0.05, preadolescents vs. adolescents

As shown in Figure 2, the comparison of HOMA-IR comparing the degree of obesity did not reveal any statistical significance (p > 0.05).

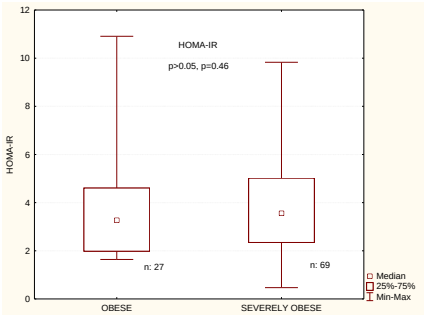

Figure 2: Homeostatic model assessment of insulin resistance comparison between obese and severely obese children and adolescents

Figure 3 shows differences in the frequency of insulin resistance (HOMA – IR > 3.16) among obese and severely obese participants. There was no statistical significance in the distribution of insulin resistance between two examined groups (p = 0.73, Pearson $\chi^2 = 0.12$, df = 1).

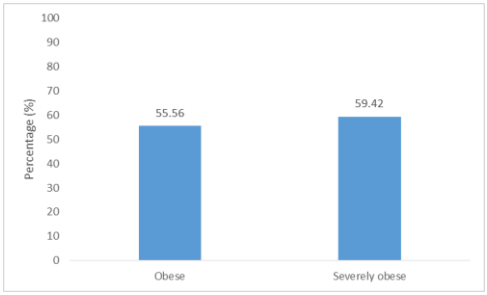

Figure 3: Frequency (%) of elevated HOMA-IR according to the degree of obesity. HOMA-IR, homeostatic model assessment for insulin resistance. p-value > 0.05, obese vs. severely obese

Correlation analysis between the BMI and HOMA-IR of the participants with age and other investigated metabolic parameters is presented in Table 4. BMI was positively correlated with age, FI and HOMA IR of the participants, while HOMA-IR showed a positive correlation with age, fasting plasma glucose, fasting insulin, triglycerides, and BMI.

Table 4: Correlation between Body Mass Index and HOMA-IR with various parameters studied

Variable	n	Body Mass Index: Correlation coefficient	Body Mass Index: *p*-value	HOMA-IR: Correlation coefficient	HOMA-IR: *p*-value
Age (years) ††	96	0.62	0.000	0.29	0.005
FPG (mmol/L) †	96	0.02	0.80	0.24	0.02
2-h G (mmol/L) †	93	0.13	0.22	0.20	0.06
FI (uU/mL) ††	96	0.34	0.000	0.98	0.00
TC (mmol/L) †	88	-0.003	0.98	0.17	0.12
TG (mmol/L) ††	88	0.16	0.14	0.38	0.000
BMI (kg/m^2) ††	96	-	-	0.33	0.001
HOMA-IR††	96	0.33	0.001	-	-

†Correlation examined using Pearson correlation, †† Correlation examined using Spearman correlation; FPG, fasting plasma glucose; 2-h G, plasma glucose two hours post the glucose load during the oral glucose tolerance test; FI, fasting insulin level; TC, total cholesterol; TG, triglycerides; BMI, Body Mass Index; HOMA-IR, homeostatic model assessment of insulin resistance.

Discussion

Studies have shown an association of excess adipose tissue with insulin resistance [30]. In the present study, 58.13% of all participants were insulin

resistant. Significantly higher percentage of girls (70.59%) was insulin resistant in comparison with boys (44.44%). A high percentage of insulin resistance among children and adolescents is also evident in other studies [31] [32]. Others have also reported that there is a significantly higher percentage of girls with insulin resistance [33]. The concentrations of plasma insulin and HOMA-IR indicating insulin resistance were not significantly higher in girls [34]. A study that aimed to evaluate possible predictors for fasting insulin levels in overweight and obese adolescents concluded that gender, BMI and waist circumference were predictors of fasting insulin and HOMA-IR. In the same study, girls were considered to have higher fasting insulin levels compared to boys [32], which is by our study results.Similarly, the level of serum insulin showed high association with female gender in a study conducted by Hrafnkelsson et al. [35]. Results from another study from the United Kingdom revealed that 5 years old girls were more prone to be insulin resistant compared to their peers of the opposite gender [36]. A study conducted on 3,203 children and adolescents from China showed that those participants with the highest number of metabolic abnormalities had significantly higher HOMA-IR [31]. Insulin resistance was significantly higher in girls [37].

We found a significant difference in gender distribution between IR and non-IR group. Namely, 64.29% of the IR group were girls, and 35.71% were boys, while 37.5% and 62.5% of the non-IR group were girls and boys, respectively. Thus, the percentage of girls was higher in the group of children and adolescents with insulin resistance. In the current study, obese girls were not found to have significantly higher values of triglycerides. Also, the frequency of abnormal triglyceride level was not significantly different compared to obese boys. Different studies have shown that insulin resistance could lead to various abnormalities affecting lipid and lipoprotein levels [2]. Contrary to our study, triglyceride levels were highly associated with female gender and were significantly higher in girls [35]. The study conducted on 151 overweight youths found that triglycerides level, as a cardiovascular risk factor, increased with the increase of fasting insulin as well as with the increase of 2 hours insulin [38]. A significant positive correlation between the level of triglycerides and fasting insulin and HOMA-IR has been confirmed in a study on overweight and obese adolescents [32]. Children who had insulin levels in the highest quartile showed increased levels of various cardiovascular risk factors such as triglycerides, systolic and diastolic blood pressure, LDL-cholesterol, VLDL cholesterol, glucose, and decreased the level of HDL-cholesterol. These children also showed higher BMI [39].

Because 52.94% of the girls were in the adolescent age, while 68.89% of the boys were in the preadolescent age, these differences in the insulin resistance status in girls might be related to the age of the participants. Namely, significantly higher percentage (51.79%) of the study participants with insulin resistance were adolescents and 70% of the non-IR group were preadolescents. Our study indicated that insulin-resistant participants had higher BMI and were older. Similarly, the mean age and BMI of study participants with IR were found to be higher compared to those without IR in a study conducted by Romualdo et al. [33]. One study on 196 obese children and adolescents from Turkey revealed that the frequency of cases with insulin resistance differs significantly between the prepubertal and pubertal group and that it is higher among obese adolescents [40]. This is also our observation. One of the most relevant longitudinal studies that was investigating insulin resistance in different stages of puberty on 357 normal children and adolescents found that up to the Tanner stage 2 insulin resistance increases, while during Tanner stages 2, 3 and 4 is constant, followed by a decrease in the prepubertal level at the Tanner stage 5 [37]. Similarly, another recent study suggests that insulin resistance is under the influence of puberty only in Tanner Stage (TS) 1, while during TS 2-4, insulin resistance did not reveal such association. Authors discuss that it could be a result of the degree of obesity, as a contributor to the development of insulin resistance, during adolescence. Therefore, screening for IR is highly recommended in children with early puberty onset, as well as, in adolescents with obesity [41]. However, the suggested insulin sensitivity recovery phenomenon in lean children at the end of puberty could not be seen in obese individuals [42] [43]. Insulin resistance during puberty in obese children is even higher than normal -weight controls [43]. Furthermore, the above-discussed decrease in insulin sensitivity has been shown to start before the pubertal transition in children with morbid obesity, and this could not be explained by total adiposity status [44]. Others have demonstrated that metabolically healthy obese children tend to change to metabolically unhealthy when growing from pre-pubertal to pubertal stage. The metabolic set up in girls could be under the influence of hormonal changes during puberty and adolescence or due to gender-specific body fat distribution [32]. It has been discussed that insulin resistance is not always a consequence of obesity, but it could also be a contributing factor that leads to its development [31]. In the USA more than 50% of the adolescents with obesity are insulin resistant [45]. In girls, insulin resistance occurring during puberty could be worsening as a result of existing obesity [46].

In the current study, an obvious unfavourable metabolic profile was noticed among insulin-resistant participants compared to the non-insulin resistant group. More precisely, participants in the IR group had higher values of all investigated laboratory parameters such as: fasting plasma glucose, 2-h plasma glucose, fasting insulin, and total serum cholesterol and triglyceride level. However, significant differences were only seen in 2-h plasma glucose, fasting insulin

and triglyceride levels. Moreover, the frequency of abnormal fasting insulin and triglycerides was higher among insulin-resistant participants. Strikingly, 96.64% and 39.62% of insulin-resistant participants tend to have elevated levels of fasting insulin and serum triglycerides, respectively. Only for comparison, the percentage of abnormal fasting insulin and serum triglycerides in the non-insulin resistant group was 12.5% and 25.71% respectively. In one study it has been shown that glucose and insulin levels among obese participants with elevated HOMA-IR (> 2.5) were significantly higher compared to the obese children with HOMA-IR below 2.5. Interestingly, these same differences were found in the non-obese participants with HOMA-IR > 2.5 and HOMA-IR < 2.5. In contrary to our results, in obese and non - an obese group with HOMA-IR < 2.5 or HOMA-IR > 2.5 participants' BMI values did not differ significantly [47]. Our study results are similar to those of Atabek et al. [40] whereas insulin resistant group of obese children have significantly higher mean age, higher BMI, fasting glucose, fasting insulin levels and HOMA-R. Triglyceride levels and total cholesterol levels were not found to differ significantly between these two groups. In Another study, triglyceride levels were significantly higher in participants with insulin resistance [33]. The differences between triglyceride levels were significantly higher in the groups of obese children and adolescents with insulin resistance compared to non-insulin resistant groups [41] [48].

The present study indicates that, although weakly, the HOMA-IR was positively correlated with the age, fasting plasma glucose levels, triglyceride levels, and BMI of the participants. Similarly, a study conducted by Esteghamati et al. [49], showed a positive correlation between HOMA-IR and BMI in all subjects as well as in different study groups considering the degree of obesity. Our study revealed the strong positive correlation between HOMA-IR and fasting insulin levels in study participants. A study that evaluated the correlation of insulin resistance assessed by different indices such as McAuley, HOMA and QUICKI, came to a conclusion that fasting insulin is sensitive and could be used as a simple test for the detection of insulin resistance in obese individuals [50]. Thus, it could be concluded that obese insulin-resistant individuals show significantly worse metabolic profile compared to non-insulin resistant ones.

Interestingly, 2.22% of boys from our study had impaired fasting glucose, while girls were not affected. On the contrary, impaired glucose tolerance was detected in 4.17% of girls, while the percentage of boys remained unchanged 2.22%. The study of Valerio et al. [51], did not detect any case of impaired fasting plasma glucose, presenting this laboratory parameter as insensitive. However, this same study found 4% prevalence of impaired glucose tolerance among the study population of obese children and adolescents. Our results are consistent with a study in which impaired fasting glucose was detected only in boys (3%), while no cases were detected in girls. Similarly, the percentage of impaired glucose tolerance among girls increased dramatically and was equal to the one among boys (11%) [52].

Hagman et al. in her studies pointed out those regional differences in glucose levels exist. A study that compared the plasma glucose level between Swedish and Polish children concluded that obese Swedish children have higher glucose levels in comparison to obese children from Poland [53]. Also, the risk of having impaired plasma glucose is higher in obese children from Sweden compared to obese children in Germany [54]. Another study conducted on 54 obese children confirmed that obese children with insulin resistance have higher blood sugar level compared to those obese children without insulin resistance [55]. Interestingly, it has been suggested that the risk of having impaired glucose tolerance is higher in obese children who have high fasting blood glucose level, but still in the range of the reference values [56].

Data from our study showed that the frequency of impaired fasting glucose, as well as impaired glucose tolerance 2 hours post oral glucose tolerance test performance, in both IR and non-IR group, were low. Only 1.79% insulin-resistant participants showed impaired fasting glucose. Similarly, 1.85% and 5.13% had impaired glucose tolerance in IR and non-IR study group, respectively. There were no cases of type 2 diabetes mellitus detected. Our results did not reveal a significant difference between plasma glucose level between IR and non-IR group. Although the prevalence of type 2 diabetes is low, studies have shown that there is a significant increase in recent years, especially with the increase in the prevalence of obesity [57].

Considering the degree of obesity, HOMA-IR values, as well as all other metabolic parameters, did not differ significantly between severely obese and obese participants. However, although differences between these two categories of obesity regarding insulin resistance did not reveal significance, it is worth mentioning that insulin resistance is high among obese and severely obese participants. Namely, 55.56% of obese and 59.42% of severely obese children and adolescents in our study were insulin resistant. The high percentage of insulin resistance among obese children is also seen in studies from the literature. Insulin resistance was found in 44.3% [52], 40.8% in obese children and 41.2% in obese adolescents [51]. A study on forty obese patients revealed that the degree of omental white adipose tissue fibrosis in severe obesity might be the explanation for the degree of insulin resistance in severely obese individuals [58]. A study found that serum insulin levels were higher among overweight children compared to normal weight children [35]. Importantly, the metabolic profile between overweight and obese subjects might not always lead to

significant differences, indicating that metabolic disturbances are already present in the overweight state [59].

We found that obese children and adolescents have a high rate of insulin resistance and have altered biochemical metabolic parameters. Lack of control group and relatively small sample size were major drawbacks of this study, therefore imposing that these data need to be confirmed in a controlled trial in order more relevant clinical conclusions to be drawn.

In conclusion, insulin resistance is highly prevalent among obese children and adolescents. Interestingly, the degree of obesity does not seem to play an important factor. Significantly higher percentage of insulin-resistant participants was girls. Also, the frequency of insulin resistance was higher among adolescents. Obese individuals with insulin resistance show more unfavourable metabolic setup, with higher BMI, plasma glucose two-hour post glucose load during the OGTT and higher levels and frequency of abnormal serum triglycerides. It is of note that the more pronounced insulin resistance was also linked with the highest concentrations of triglycerides.

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Case Report

Acupuncture Treatment of Subfertility and Ovarian Endometrioma

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Abstract

BACKGROUND: Ovarian endometriotic cysts, also known as 'chocolate' cysts or ovarian endometriomas, appear as endometrial tissue outside the uterine cavity which grows inside ovaries. Endometriotic cysts can cause chronic pelvic pain, dysmenorrhea, dyspareunia, impairment of ovarian function in regards to subfertility, etc. Traditional Chinese Medicine (TCM) is effectively treating subfertility associated with endometriosis for years, and the treatment gives positive results in achieving pregnancy. With the acupuncture treatment, blood circulation is promoted, external physical factors - eliminated, the stasis is dissolved, the menstrual cycle is regulated, and inflammation is diminished.

CASE REPORT: Our treated patient is 29-year-old woman diagnosed with ovarian endometrioma, slightly - elevated prolactin levels and inability to get pregnant after trying for two years. Ningteen acupuncture treatments were done on the meridians of Pericardium, Spleen, Stomach, Liver, Ren Mai, Kidney, Large intestine, Du Mai and Bladder. After the acupuncture treatments, the endometrioma was decreased in size and the patient got pregnant spontaneously in a short period.

CONCLUSION: Acupuncture, as part of the TCM, gives positive results and can successfully add up to variety of non - surgical infertility treatment options in women with endometrioma(s).

Introduction

Ovarian endometrioma is a benign, estrogen-dependent endometriosis cyst found in women of reproductive age. Infertility/subfertility is associated with ovarian endometriomas; although the exact cause is unknown, oocyte quantity and quality are thought to be affected. **"**Chocolate" endometriotic cysts occur in 10% of women in the most reproductive years from the age of 25 to 40. The most common locations of endometrial cells implantation are in the ovaries and the peritoneum [1]. These cysts are filled with brown - coloured unclotted thick old blood resembling liquid chocolate, so that's why they are called 'chocolate' cysts. Some cysts do not cause any symptoms, but some cause problems like irregular periods, pain and even infertility [2]. Symptoms that may occur are very painful periods, excessive swelling during the period, low - abdominal cramping, painful sexual intercourse or pain during physical activity, chronic pelvic pain, etc. [3]. TCM treats a wide range of disorders including infertility due to ovarian endometriomas. Regarding TCM, ovarian cysts may present with kidney yang and yin deficiency (kidney energy is responsible for human reproduction), and if the energy is weak to circulate and warm the blood, it will stagnate. Cysts also may present with liver Qi stagnation or can be caused by excessive dampness, which is caused by fluid and blood stasis and, accumulated in the abdomen, it slowly becomes phlegm. Regarding TCM, if the blood doesn't circulate properly and freely throughout the body, then blood stagnation occurs, leading to disease. Some scientists say that endometriosis is an autoimmune disease, although this is neither well understood nor proven. However, autoimmune diseases can be dissolved with series of acupuncture treatments. Acupuncture improves immune response and liver function, which stimulates the nervous system to release neurotransmitters and hormones, reduces stress, improves the blood and energy circulation throughout

the whole body, reduces the chances of blood stagnation (which causes infertility and pain) and balances the energy in the body [4] [5].

Case report

Our patient is a 29-year-old woman, with body mass index of 20, non - smoker, a lawyer, with no previous history of the abdominal surgeries, diagnosed with primary subfertility and endometrioma of the left ovary. The couple was unable to achieve pregnancy after trying for two years. Before coming to our TCM outpatient clinic, the patient has visited a couple of outpatients – medical –office - gynaecologists for fertility tests. The investigations are shown, as follows. PAP smear was normal, and microbiology swabs' cultures were negative. All program parameters were within normal limits, thus excluding the male factor of infertility. 3rd – day – menstrual - cycle hormonal panel (FSH, LH, E2, PRL, TSH, T3, T4) showed results within reference ranges for the age and the menstrual cycle phase, with the exception of slightly-elevated prolactin, measuring PRL = 32.7 ng/mL (ref. range 1.9 - 25.0 ng/mL). No anti – Mullerian - hormone (AMH) measurements were done, but transvaginal ultrasound (TVUS) antral follicle count (AFC) was 13. Few months' series of 2D/3D/4D transvaginal ultrasounds (with foliculometry) proved existence of normal ovulatory regular menstrual cycles (sonohysterography showed normal size and morphology of uterine cavity, and serial TVUSs showed proper endometrial thickness during periovulatory days, presence of monthly ~20 mm leader - follicle in the right or in the left ovary as well as ultrasound signs of ovulation in both ovaries interchangeably, regular presence of corpus luteum in the luteal phase, besides the constant presence of one endometriotic cyst measuring 37.8 x 23.9 mm in the left ovary (Figure 1), with a typical endometrioma appearance of homogenous low - level internal echoes and thick walls).

Figure 1: Endometrioma 38 x 24mm, left ovary, before acupuncture treatment

Both gynaecologists, separately, suggested hysterosalpingography or laparoscopic (LPSC) examination of tubal patency together with simultaneous LPSC removal of the cyst, but the patient rejected the suggestion for X-ray diagnostic and invasive surgical procedures (due to personal preferences) and decided to turn to acupuncture treatment. The patient opted only for acupuncture, as a treatment option of couple's subfertility. Nineteen acupuncture treatments were done in 4 months, starting from 29th March until 26th July 2016. Acupuncture treatments were done once a week, in a TCM and Acupuncture Outpatient Clinic in Skopje, Republic of Macedonia, by a licensed medical doctor - specialist in TCM and acupuncture, on room temperature, with 35 - 40 minutes duration.

Figure 2: Endometrioma and folicules, left ovary, before treatment

Fine sterile disposable 0.25 x 25 mm needles were used for the treatment (manufactured by Wuijuiang City Medical & Health Material Co., LTD). Acupuncture treatments were being done in points located on the meridians of Pericardium, Spleen, Stomach, Liver, Ren Mai, Kidney, Large intestine, Du Mai and Blader. The couple was advised to continue with regular spontaneous intercourses during periovulatory days of the cycle. After only 4 months of acupuncture treatments, the couple achieved spontaneous pregnancy. Follow - up TVUS showed viable intrauterine one – embryo - pregnancy and yellow body of pregnancy on the left ovary, as well as a decrease of the left - ovarian endometriotic cyst dimensions to 24.2 x 22.2 mm (Figure 3).

Figure 3: Reduced endometrioma 24x22mm, left ovary, after acupuncture treatment

Discussion

A condition such as infertility can be very scary, emotionally draining and disappointing for young couples, especially for women who are trying to conceive pregnancy for the first time. Ovarian cysts appear mostly during a woman's childbearing years. Some cists are functional and benign, but some are cancerous [6]. In our case, the patient had benign left - endometriotic ovarian cyst (Figure 2), with normal, ovulatory, regular, but very painful, menstrual cycles, without even knowing such cyst existed. Several investigations and ultrasound images of the ovaries and uterus had been done, due to unsuccessful spontaneous attempts to conceive a pregnancy, which lasted for 2 years. TVUS images showed visible endometriotic cyst of the left ovary and lab investigations showed slightly elevated prolactin levels. Ovarian cysts don't always manifest symptoms like chronic lower abdominal pain, breast tenderness, irregular menstrual periods, nausea, dizziness, painful sex (which is a case in our patient), but according to the TCM there are other symptoms and physical signs that can identify possible presence of cysts, such as pale tongue, poor appetite, depression, mood swings, constipation/diarrhea, pale face, sweating, etc. TCM suggests a couple of additional causes for endometriomas, such as stress as well as spleen, kidney, liver and lung Qi deficiency [7]. Also, the three main pathological factors that may affect the development of ovarian cysts according to TCM are blood stasis, phlegm and dampness, and each of these factors needs time to develop. Dampness and phlegm appear due to imbalanced spleen energy. The excessive dampness in the system gradually transforms into phlegm and manifests in the body as masses, lumps and cysts of various kinds, including ovarian cysts. The diet is the key for good kidney health - no alcohol, sweets, fatty, raw and cold food and beverages, only warm liquids and cooked vegetables. The major factor in causing infertility and cysts is the blood stasis when the blood is not flowing easily and smoothly along the pathways. The pain is always a side effect of blood stagnation, and the liver is the organ where the stasis is forming because of the liver stores blood and regulates menstruation [8]. The acupuncture points located on the meridians of Pericardium, Spleen, Stomach, Liver, Ren Mai, Kidney, Large intestine, Du Mai and Blader are chosen so to bust the yang energy, nourish the kidneys, disperse stagnation, move the blood stasis, tonify the kidneys, transforms the phlegm and dampness and important immune factors which protect the placenta and the embryo are increased [9] [10].

Moreover, the patient option to choose a mode of non - invasive (less - invasive) non - surgical 'expectant management' and treatment with acupuncture maybe found its justification in the ongoing controversy on the surgical treatment of endometriomas: whether to operate them or not? Accepted guidelines say that the surgical removal of endometriomas is not an absolute necessity in all cases of infertility before starting with infertility treatments [11]. The laparoscopic cystectomy procedure strips the cyst wall – the portion of the cyst containing the endometrial tissue. The benefits of this procedure include decreased recurrence rates, a significant reduction in pelvic pain and increase in spontaneous pregnancy rates following surgery, due to decreased ovarian inflammation which can lower follicular density. However, the main controversy associated with cystectomy is that it damages or removes healthy ovarian cortex and follicles, leading to a decrease in ovarian reserve following the procedure. In a meta-analysis comparing eight studies of ovarian endometrioma surgical treatment, the patients who had either unilateral or bilateral cystectomy had significantly lower AFC and AMH levels following the surgery than before it. Ovarian failure, a serious risk associated with cystectomy, has been reported after bilateral endometrioma cystectomy, with rates ranging from 2.3 to 3.03%. In addition to potentially removing healthy cortex, inflammation after surgery could further damage the cortex or decrease vascularisation. The damage caused by scar tissue may reduce the volume of the healthy ovary, and scar tissue may interfere with oocyte retrieval later on [12]. Furthermore, the European Society of Human Reproduction and Embryology ESHRE recommend laparoscopic surgery only in the treatment of endometriomas that are more than 4 cm in diameter, which is not a case in our patient. Many studies show that there is the difference in fertilisation/implantation/clinical pregnancy rates between patients with and without the presence of ovarian endometriosis [13]. But non - surgical 'expectant' management is also an optional potential treatment plan, as recent literature suggests that ovarian endometriomas do not negatively affect IVF/spontaneous pregnancy outcomes. However, much more research is needed to establish how ovarian endometriosis management affects infertility treatments and gross perinatal outcomes [11] [13].

In conclusion, acupuncture, as part of the TCM, gives positive results and can successfully add up to variety of non - surgical infertility treatment options in women with endometrioma(s). With the acupuncture treatments, we succeeded both to help patient get pregnant spontaneously in a short period, as well as to decrease dimensions of the ovarian endometrioma.

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Case Report

The Effectiveness of Radial Extracorporeal Shock Wave Therapy for Chronic Achilles Tendinopathy: A Case Report with 18 Months Follow-Up

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Abstract

BACKGROUND: Achilles tendinopathy (AT) is a pathological state resulting from repetitive loading or stress on the tendon. The article aims to evaluate the effects of the low - energy radial extracorporeal shockwave therapy (RESWT) in the treatment of the adult with chronic insertional Achilles tendinopathy (AT) after the unsuccessful conservative treatment, with 18 months follow - up evaluation.

CASE REPORT: We report the case of a 55 years - old male suffering from severe right posterior heel pain for 4 months. For his chronic insertional Achilles tendinopathy on the right heel, he received conservative treatment in the Institute of Physical Medicine and Rehabilitation. For outcome assessment, Numerical Rating Scale (NRS) for pain, the range of motion in the ankle, and Roles-Maudsley Score (RMS) for assessment of function were used. At the baseline the pain was severe, and he received physical therapy treatment. After unsuccessful conservative treatment, he underwent RESWT treatment. Numeric Rating Scale was significantly decreased at immediate, short-term and long-term follow-up. After the last treatment, the patient had no pain, and function assessed by Roles-Maudsley Score was excellent. At the follow-up check-up at 3, 6, 12 and 18 months the patient had no pain and excellent functional results.

CONCLUSION: Radial ESWT is a safe and effective treatment even for a longer period for patients with chronic insertional Achilles tendinopathy.

Introduction

Achilles tendinopathy (AT) is a pathological state resulting from repetitive loading or stress on the tendon [1]. The two main categories of Achilles tendon disorder are broadly classified by anatomical location to include non - insertional and insertional conditions [2].

This clinical condition is characterised by pain and tenderness in or around Achilles tendon, frequently occurring in active, as well as, inactive individuals [3]. Chronic Achilles tendinopathy was defined as a condition lasting more than six weeks [4] or more than three months [1]. Chronic Achilles tendinopathy has been described as the most common overuse injury in sports medicine [5].

Several treatment modalities such as activity modification, heel lifts, arch supports, stretching exercises, nonsteroidal anti-inflammatories, and eccentric loading are known as standard conservative treatment [4] [5] [6], as well as various injections and extracorporeal shock wave therapy (ESWT) [2].

In chronic refractory cases that exhibited no improvement after appropriate conservative treatment, surgical intervention has been performed [5] [6] [7].

Extracorporeal shock wave therapy (ESWT) has been successfully used in soft - tissue pathologies like lateral epicondylitis, plantar fasciitis, and calcific

tendinopathy of the shoulder, Achilles tendinopathy and also in bone and skin disorders [5].

Radial extracorporeal shock wave therapy (RESWT) is the application of high-intensity acoustic radiation, (high - energy acoustic waves - shock waves). Shock waves are defined as a sequence of single sound pulses which are characterized by high point of pressure that can reach up to 100 MPa (but most often 50 - 80 MPa), fast reach of pressure for a short period of less than 10ns, short duration (10 μs), followed by a variable negative pressure that can affect cavitation and a frequency of 16 - 20 Hz [8] [9].

Last decade some article about the effectiveness of extracorporeal shock wave therapy as management of chronic Achilles tendinopathy had been published [10] [11] [12].

The mechanism by which ESWT may produce a clinical effect is still uncertain. Several theories have been proposed: a mechanical effect by increasing the pressure in the calcium deposition causing fragmentation; a molecular effect with induction of an inflammatory response with neovascularisation and then a chemotactic action and phagocytosis of calcific deposits; an analgesic effect by inhibiting the activation of the serotonergic system, and peripheral denervation. Probably, a combination of angiogenic and analgesic effects explains the overall outcomes on the target tissues [13].

The article aims to evaluate the effects of the radial extracorporeal shockwave therapy (RESWT) in the treatment of an adult with chronic insertional Achilles tendinopathy (AT) after unsuccessful conservative treatment, with 18 months follow - up evaluation.

Case report

We report the case of a 55 years - old male (man) suffering from severe right posterior heel pain for 4 months. He performed recreational activities like walking, skiing, swimming, riding the boat regularly. He suffered from pain, tenderness at the Achilles tendon insertion at the back of the heel bone, with or without activity, even when he wears comfortable shoes. He underwent plain radiography. Plane x-ray radiography of the right heel showed the presence of retrocalcaneal entensophyte (bone spur) (Figure 1).

He didn't have the presence of systemic inflammatory disease; previous history of foot surgery; fracture of foot or ankle; and calcification of Achilles tendon. For his chronic insertional Achilles tendinopathy on the right heel, he received conservative treatment in the Institute of Physical Medicine and Rehabilitation.

Figure 1: Plane x-ray radiography of the right heel showed the presence of retrocalcaneal entensophyte (bone spur)

For outcome assessment Numerical Rating Scale (NRS) for pain, the range of motion in the ankle, and Roles - Maudsley Score (RMS) (12) for assessment of function were used. Numerical Rating Scale is an 11 - point pain intensity rating scale, where 10 points indicate worst possible pain and 0 points no pain.

The immediate follow - up (1 week after the last RESWT), short-term outcome (after 3 and 6 months) and long-term outcome (after 12 and 18 months) were analysed. The assessments were performed at baseline, at the end of the treatment, 1 week and 3, 6, 12 and 18 months after completion of the treatment.

At the baseline the pain was severe, Numeric Rating Scale 7 points, and his functioning was assessed with Roles - Maudsley Score as poor (point 4, pain - limited activities), the range of motion in the right ankle was in normal range (dorsal flexion 20 degrees, plantar flexion 30 degrees bilaterally). He had pain on palpation in the area of the insertion of Achilles tendon. He received physical therapy treatment with therapeutic ultrasound, iontophoresis with anaesthetic (novocaine), and stretching calf exercises during two weeks (10 sessions with weekend pause).

After that treatment, he had some improvement with some decreasing of pain (Numeric Rating Scale 5 points) and small functional improvement Roles - Maudsley Score as fair (point 3, some discomfort after prolonged activity). After unsuccessful conservative treatment one week later he underwent on low energy radial extracorporeal shock wave treatment.

RESWT protocol

For the application of the radial extracorporeal shock wave therapy the device BTL - 5000 SWT Power (BTL Industries Ltd., United Kingdom) was used, with 15 mm radial probe. Shockwave was

applied to the area of maximal tenderness (over the insertion) at Achilles tendon with the patient lying in the prone position.The therapy was applied by the recommendations of the manufacturer: continuous type of the shocks, with 2000 shocks per session. The shocks were applied with a pressure of 2 Bar and a frequency of 10 Hz. The low energy was used, so the application was painless and required no anaesthesia or analgesics. A total number of treatment sessions were 5. The time interval between treatments was one week. RESWT was used as a single intervention.

The patient was educated to perform home-based Achilles tendon stretching exercise and recommended to reduce activity level, to avoid impact activities, such as running and to wear comfortable, soft leather shoes.

Numeric Rating Scale was significantly decreased at immediate and long-term follow-up. Between the treatments sessions, the patient reported decreasing the pain level and improvement of functioning. After the last treatment, the patient had no pain (Numeric Rating Scale was 0 point), and there was an improvement of function Roles - Maudsley Score was excellent (point 1, no pain, full movement and activity). At the follow - up check - up at 3 months, 6 months, 12 and 18 months the patient has no pain and excellent functional results. He was involved in all previous work duties and recreational activities.

Discussion

In our study, we report the immediate, short - term and long - term effectiveness of low - energy radial extracorporeal shock wave therapy in a patient with chronic insertional Achilles tendinopathy.

Achilles tendinopathy may be insertional or non - insertional (mid - portion) tendinopathy. Non - insertional Achilles tendinopathy is often managed conservatively, and many rehabilitation protocols have been adapted and modified, with excellent clinical results. The management of insertional Achilles tendinopathy with conservative rehabilitation protocols as used in non - insertional disorders were thought to prove less successful [2].

For chronic Achilles tendinopathy (symptoms lasting longer than six weeks), an intense eccentric strengthening program of the gastrocnemius/soleus complex improved pain and function between 60 and 90 percent in randomised trials [4].

In the management of chronic tendon injuries, other modalities such as prolotherapy, topical nitroglycerin, iontophoresis, phonophoresis, therapeutic ultrasound, extracorporeal shock wave therapy, and low - level laser therapy have less evidence of effectiveness but are reasonable second-line alternatives to surgery for patients who have persistent pain despite appropriate rehabilitative exercise [4].

Treatment such as extracorporeal shock wave therapy is also proving successful [2]. Our patient had significant improvement with decreasing of heel pain and improvement of the function at short-term (3 and 6 months) and at long-term follow - up (12 and 18 months).

Most of the studies regarding usage of ESWT in patients with chronic Achilles tendinopathy reported short-term 3 or 4 months [10], 6 months [14] or long - term 12 months outcome [10] [11] [12]. We used low - energy radial extracorporeal shock wave therapy.

Recently published data have shown the efficacy and low - energy [10] [11] as well as of focused extracorporeal shock wave therapy [15] in chronic Achilles tendinopathy.

In our study, a maximum of 5 sessions of low - energy radial ESWT (Bars, 10 Hz, 2000 shocks per session, weekly) were conducted until the patient reached “excellent” treatment success.

In the reported studies, Rompe et al. treatment protocol included 3 sessions of low - energy ESWT using 0.12 mJ/mm^2 with 2,000 shocks per session [10], Pavone included 4 sessions of low - energy ESWT with a 2 - week interval, from 800 shocks in each one (4 Hz, 14 KeV) [11]; Lee et al. included a maximum of 12 sessions of ESWT (0.10 - 0.11 mJ/mm^2, 600 shocks, weekly) were conducted until Roles - Maudsley Score reached ‘good’ or ‘excellent’ (treatment success), [12]; while Furia performed just a single session of ESWT using high - energy (0.21 mJ/mm^2) with 3,000 shocks [15].

In the randomised, controlled trial of 50 patients with chronic (6 months or more) recalcitrant insertional Achilles tendinopathy eccentric loading showed inferior results to low - energy shock wave therapy as applied in patients with chronic recalcitrant tendinopathy of the insertion of the Achilles tendon at four months of follow - up. The favourable results of repetitive low - energy shock wave therapy at four months were stable at the one - year follow - up evaluation [10].

Pavone V et al. reported the results of a series of 40 patients with chronic insertional Achilles tendinopathy treated with low - energy ESWT after the failure of a 3 - month program of eccentric exercises alone. All patients were previously treated with only eccentric exercises for a 3 - month period. The treatment protocol included 4 sessions of ESWT with a 2 - week interval, from 800 shots in each one (4 Hz, 14 KeV), together with eccentric exercises. At the 12 - month follow - up, 26 (65.0%) patients did not complain about pain (VAS < 2), 11 (27.5%) patients got back to normal activities

despite residual pain (VAS 2 - 4), and 3 (7.5%) of the patients still complained about pain (VAS > 4). There was no significative improvement in both scores after eccentric exercises alone [11].

Costa ML et al. in the randomised placebo-controlled trial with forty - nine patients with Achilles tendon pain who were treated with ESWT once a month for 3 months, at the end of the trial, they found no difference in pain relief between the shock wave therapy group and the control group [16].

Furia JP, reported one month, 3 months, and 12 months after treatment that group of patients with chronic insertional Achilles tendinopathy who were treated with 1 dose of high-energy extracorporeal shock wave therapy had significant reduction of pain on Visual Analogue Scale compared with a group of patients who were treated with nonoperative therapy. Twelve months after treatment, the number of patients with successful Roles and Maudsley scores was statistically greater in the ESWT group compared with the control group, with 83% of ESWT group patients having a successful result [15].

In the systematic review of 4 prospective randomised controlled trials and 2 prospective clinical trials with a minimum 3 months' follow - up, Al - Abbad H, and Simon JV, investigated the effectiveness of ESWT in the treatment of insertional and noninsertional Achilles tendinopathies. Four out of six studies reported statistically significant improvement with ESWT in pain scores at a minimum of four months period, and also four of five studies reported statistically significant improvement in functional outcome with ESWT. Overall, their review showed satisfactory evidence for the effectiveness of low - energy ESWT in the treatment of chronic insertional and noninsertional Achilles tendinopathies at a minimum 3 months' follow - up before considering surgery if other conservative management fails. However, combining ESWT with eccentric loading appeared to show superior results [1].

Our patient had the good immediate therapeutic effect of RESWT although his plane x-ray showed the presence of retrocalcaneal entensophyte. Presence of retrocalcaneal enthesophyte may imply that the patient has high activity level and is more liable to overuse injuries.

Retrocalcaneal enthesophytes may be an adaptive response to increased traction in the Achilles tendon [17]. Increased mechanical loading triggers osteoblastic activity at the tendon attachment site, and physically active people are more likely to exhibit the presence of enthesophytes [18].

In the recently published study, Lee JY et al. investigated immediate and long-term outcome (mean 26 months) in 36 patients who underwent ESWT for chronic (> 6 months) AT after unsuccessful conservative treatment. They concluded that ESWT appeared to be effective in achieving long-term success. Immediate success was associated with the absence of retrocalcaneal enthesophyte on X-ray, the presence of pretreatment abnormal ultrasonography echogenicity, shorter mean duration of 'post-treatment soreness', and shorter duration of 'post -treatment soreness after first ESWT'. The shorter duration of 'post - treatment soreness after first ESWT' was identified as the only positive prognostic parameter in achieving long - term success [12].

There were no adverse effects of application of radial ESWT in our patient.

Costa ML et al. in the randomized placebo - controlled trial reported that there were two patients (62 years and 65 years) with tendon ruptures in the treatment group, suggesting caution when treating older patients [16].

In the retrospective clinical study with 67 patients were compared the results of extracorporeal shock wave therapy (ESWT) for insertional Achilles tendinopathy with or without Haglund's deformity. Authors reported that ESWT resulted in greater clinical outcomes in patients without Haglund's deformity compared with patients with Haglund's deformity [19].

In conclusion, radial extracorporeal shock wave therapy is a safe and effective treatment even for longer period of time for patients with chronic insertional Achilles tendinopathy if conservative treatment fails. Further research is warranted to better define the appropriate dosage, interval of treatments, number of sessions to achieve excellent and good clinical outcome.

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Case Report

Microperforated Hymen Presenting Spontaneous Pregnancy with Cesarean Delivery and Hymenotomy Surgery: A Case Report

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Keywords: Cesarean Delivery; Imperforate Hymen; Hymen Incision Surgery

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Abstract

BACKGROUND: Female genital tract anomalies including imperforate hymen affect sexual life and fertility.

CASE PRESENTATION: In the present case, we describe a pregnant woman diagnosed with imperforate hymen which never had penetrative vaginal sex. A 27–year-old married patient with 2 months of amenorrhea presented in a clinic without any other complications. Her history of difficult intercourse and prolonged menstrual flow were reported, and subsequent vaginal examination confirmed the diagnosis of imperforate hymen even though she claims to made pinhole surgery in hymen during puberty. Her urine pregnancy test was positive, and an ultrasound examination revealed 8.3 weeks pregnant. The pregnancy was followed up to 39.5 weeks when she entered in cesarean delivery in urgency. Due to perioperative complications in our study, a concomitant hymenotomy was successfully performed. The patient was discharged with the baby, and vaginal anatomy was restored.

CONCLUSIONS: This case study suggests that even though as microperforated hymen surgery in puberty can permit pregnancy and intervention with cesarean section and hymenotomy is a good option to reduce the resulting perioperative complications which indirectly affect the increase of the fertilisation and improvement of later sexual life.

Introduction

Female genital tract anomalies have an important impact on the sexual activity and fertility. Imperforate hymen is a congenital disorder of hymenal configuration which does not permit normal menstrual flow [1]. Minor surgery can fix an imperforate hymen in puberty age, even though there are reports that virginity sparing (pinhole) surgery is a solution when the hymen is a social problem in unmarried girls, and this can still lead to infertility [2]. In the present case, we describe a pregnant woman diagnosed with imperforate hymen which never had penetrative vaginal sex.

Case report

A 27 – year - an old woman complained of amenorrhea for 2 months. She had been married for 1 year and claims problems with sexual intercourse. Her menstruation periods were turned to be regular after performing virginity sparing surgery in childhood period. After clinical examination, she was conscious, oriented and normotensive. On inspection of the external genitalia, a membranous structure covering the vagina was detected, without visualisation of the cervix and taught right membrane which was associated with imperforate hymen (Figure 1a).

Her urine pregnancy test was positive, and abdominal ultrasound resulted in 8.3 weeks pregnancy (Figure 1b). Based on the clinical outcomes of the patient we did not find it applicable to make and additional surgery of hymenal ring even though the risk of its healing process during pregnancy is reported in the literature as well. The pregnancy was followed up to 39.5 weeks without any previously diagnosed and observed complications. Patient has come into the clinic with pain and uterine contractions and based on the imperforate hymen diagnosis the cesarean delivery was performed under brief general anaesthesia which resulted with successful birth (male; 3700 gram; 53 cm and Apgar score 7/8).

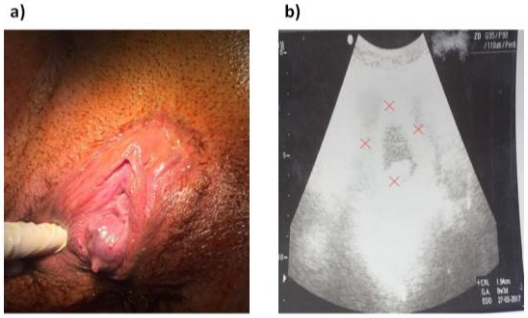

Figure 1: a) Imperforate hymen with a hymenal membrane covering the vagina (b) Transabdominal ultrasound showing gestational sac and embryo

However during the following intervention when the morbidly adherent placenta (placenta accreta) was removed, an active bleeding was observed and after unsuccessful attempting in the revision of uterus cavity and placing of two sutures in the front wall of the inner part of the uterus for hemostasis induction, we have proceed further for hemostasis induction with the incision of hymen was done (Figure 2a) in order to make full passability and the uterine cavity tamponade which later resulted with successful hemostasis and operation.

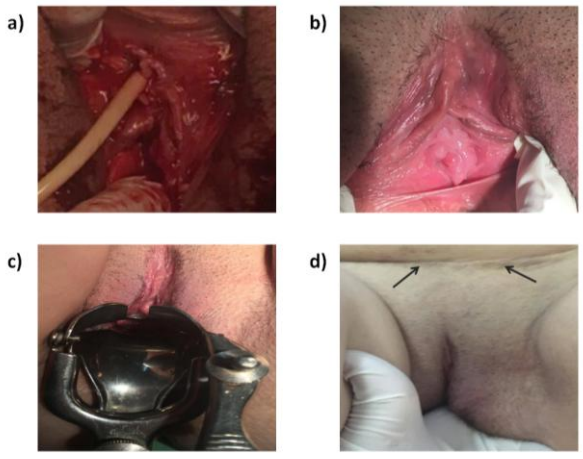

Figure 2: a) Hymenotomy surgery during cesarean delivery; b) Hymen view after surgery; c) Restoration of normal vaginal anatomy posthymenotomy d) Normal penetration and wound healing

The patient was discharged after all the treatment procedures with her baby for outpatient follow - up. At the 4 - week follow up after hymenotomy the vaginal anatomy including also normal penetration was restored (Figure 2b and c), and the cesarean wound was healed effectively (Figure 2d). Later on, the patient reported being well and had normal sexual intercourse.

Discussion

Imperforate and microperforated hymen tissue occurs during the embryologic development and is congenital anomalies. There are many symptoms which characterise this malformation including primary amenorrhea, pelvic pain, vaginal bleeding, vaginal discharge, dysuria, infertility etc. Usually, the symptoms tend to persist without an early intervention in early childhood [3]. Due to this a simple microsurgery procedure including incision of the hymen is recommended in early childhood to relieve the symptoms [4]. However, there are different cultural and religious importance to keep the intact hymen, which makes surgeon decide to keep the natural intact hymen under those circumstances [5]. Providing intact hymen by making a pinhole opening may permit passage of menstruation blood flow or semen, but still, the difficulty in having sexual intercourse or penis penetration exists, which may lead to infertility, even though consequently spontaneous pregnancy could rarely occur [6] [7]. There are rare minor reports that spontaneous closure of the hymen was done during pregnancy due to the healing process [8]. Also, an incomplete abortion is reported in microperforated hymen which shows that surgical correction is essential for long-term treatment and also sexual and psychological health [9]. In the present case, it has been shown that spontaneous pregnancy may happen without normal sexual intercourse. The closure of hymen in pregnancy was observed. There are no reports regarding the cesarean section associated with complicated bleeding and the necessity for intervention with hymenotomy. This rare case represents a successful cesarean delivery performed in concomitant with hymenotomy surgery.

In conclusion, keeping intact hymen in imperforate hymen extends the problems in sexual intercourse; this may rarely lead to spontaneous pregnancy without fetus complications. Cesarean delivery is the preferred choice in the patients with imperforated hymen patients, even though in our case the active bleeding from morbidly adherent placenta was urgency procedure and the main indicators to proceed further with hymenotomy in order to make the uterine tamponade which indirectly affects the reduction of operative possible complications of

cesarean delivery which indirectly affect the increase of the fertilization and improvement of later sexual

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Case Report

Topical Imiquimod 5% as a Treatment Option in Solitary Facial Keratoacanthoma

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Abstract

BACKGROUND: Keratoacanthoma (KA) is a rapidly growing epithelial tumour with histopathologic and clinical features similar to squamous cell carcinoma (SCC) and a certain tendency toward spontaneous regression.

CASE PRESENTATION: This article presents a unique and rare case of keratoacanthoma arising from the upper lip of a young male patient. These two features are in contrast to most of the reported cases in elder male individuals and on the lower lip. Relevant management protocol of the case has also been discussed.

CONCLUSION: The article emphasises the significance of discerning such lesions from squamous cell carcinoma thus carrying diagnostic and therapeutic implications. However, in case of the dilemma it is prudent to assume that the lesion is SCC unless proved otherwise clinically and histologically.

Introduction

Keratoacanthoma (KA) is a rapidly growing epithelial tumour with histopathologic and clinical features similar to squamous cell carcinoma (SCC) and a certain tendency toward spontaneous regression.

The etiologic factors involved in the development of keratoacanthoma are multiple. The role of UV radiation, chemical carcinogens, radiation therapy, genetic factors and various forms of antecedent trauma, including surgery, grafting, thermal burns, laser resurfacing, and vaccination have been documented [1] [2].

The lesion has a predilection for sun-exposed areas of face, neck, forearms. Lower lip location is six times more prevalent in comparison to upper lip [3].

The incidence increases with age, and it is more common after the age of 40 years with a slight predominance in males. The youngest reported is a 15-year-old patient with traumatically induced keratoacanthoma [1]. It is also more common in light-skinned persons.

The short history relative to the size of the lesion and its typical clinical course carries diagnostic importance. It begins as a rapidly enlarging nodule over a period of 4 - 5 weeks, followed by a period of stability for another 4 - 8 weeks before undergoing spontaneous involution and complete resolution over a period of 6 months to 2 years with the expulsion of keratin leaving a depressed scar [4] [5].

Keratoacanthomas show a tendency to a spontaneous resolution, and, in typical cases, some practitioners adopt the so-called watchful waiting approach, particularly in the cosmetically relevant

areas. However, KA can be easily misdiagnosed as SCC; therefore in most cases, surgical excision is considered the treatment of choice.

Case Report

A 31 – year - old Caucasian male was referred to our Maxillofacial surgery department for evaluation of a rapidly growing asymptomatic solitary nodule located on the mucocutaneous upper lip, present for the last 4 weeks.

Clinical examination revealed a well-demarcated, firm, dome-shaped nodule 1.5 cm in diameter with a small central keratinous plug (Figure 1). The patient reported that the growth developed in the site of a previous scar result of a shaving accident two years ago.

Figure 1: Patient presenting with KA of upper lip at the initial visit

Working clinical diagnosis of solitary KA was made based on the history of short duration, rapid enlargement and morphology. Neck palpation did not reveal any suspicious lymph nodes. Past medical history was positive for vitiligo for which he was not interested in evaluation or therapy. The patient did not practice photoprotection.

Subsequently, incision biopsy was performed under local anaesthesia. The histopathological evaluation confirmed the diagnosis of KA. We treated him with topical application of imiquimod cream 4 times a week. The inflammatory reaction appeared in less than 2 weeks of application. The size of the tumour had decreased considerably, and central core expulsion was noted which left central depression surrounded by epithelial tags (Figure 2).

Figure 2: The same patient after 2 weeks of treatment with topical Imiquimod 5%

After 8 weeks, the mass was markedly flattened. At week 10 of therapy further improvement was recorded. The lesion had healed with a hypopigmented scar and remaining epithelial tags. The treatment was discontinued at this point. During the follow-up visit at week 12 further improvements were noted mainly in the smaller epithelial tags (Figure 3). During the subsequent follow up visits the improvement remained stable. We performed shave biopsy of the epithelial tags. Histopathology revealed no residual tumor elements.

Figure 3: The same patient at week 12 (2 weeks after completion of treatment with topical Imiquimod 5%

The lesion was photographed sequentially and documented until complete resolution.There was no recurrence after 12 months follow - up.The patient was also advised of the importance of photoprotection and referred for a dermatological evaluation.

Discussion

KA is an epithelial neoplasm which is clinically indistinguishable from SCC and has a strong histological similarity to well differentiated SCC [5][3][6].

Some authors are of the opinion that solitary KA represents an extremely low-grade SCC [7] [6].

KA of the lip may arise from the skin rather than labial mucosa, which could well have been the case in the present patient [4] [6].

Some authors consider KA as a self-limiting and benign tumour which undergoes spontaneous resolution in contrast to SCC which is considered a biologically malignant neoplasm with a potential to metastasise and local tissue destruction [4].

Difficulties in differentiating between these two lesions are of huge importance since it carries therapeutic implications. Solitary large keratoacanthomas (KAs) of the head and neck present a management dilemma, due to the unpredictable clinical course. Therapeutic options proposed in the literature include complete excision, topical agents as podophyllin, 5 - fluorouracil and imiquimod [8], intralesional injection of bismuth, bleomycin, interferon Alfa - 2a, methotrexate [9] and triamcinolone (corticosteroids) [10], oral retinoids and photodynamic therapy, cryotherapy and radiotherapy with various outcomes [11].

Continued growth or significant pain despite the therapy, may suggest an underlying SCC in clinically classic KA. In these cases, surgery is recommended [12].

Complete surgical excision is the treatment of choice, but complete excision can be too destructive and cosmetically or functionally unacceptable for tumours on cosmetically important sites. Despite this, the recommended treatment in literature for solitary KA of the lip is surgical excision because of the concern that the lesion may be a squamous cell carcinoma and clinical as well as histological differentiation of the two lesions is difficult [13].

The advantages of surgical excision include rapid treatment and availability of a complete specimen for histologic examination.

Laser and cryotherapy as treatment modalities have some limitations as they can lead to substantial defects with functional or cosmetic morbidity, and do not allow for the histopathologic confirmation of the clinical diagnosis. Radiotherapy is an effective treatment of KA and offers the potential for a cure without requiring surgery or the need for reconstruction and has also been used as an adjunctive treatment following surgery, but it may not be advisable for younger patients, and it may pose an inconvenience due to the need for multiple hospital visits.

Systemic retinoids, such as isotretinoin, can be considered for patients with multiple lesions for which surgery is not adequate treatment modality.

Intralesional methotrexate (MTX), 5 - fluorouracil, bleomycin, and steroids have all been used with success in patients who are either poor surgical candidates or have lesions not amenable to surgery because of size or location [10]. A 2007 review of the use of intralesional injection of MTX on 38 patients, showed a 92% clinical "resolution" rate. However, patients needed an average 2.1 injections to achieve it [9].

Intralesional methotrexate and 5 - FU have also been recommended for extensive lesions or lesions in more cosmetically sensitive areas, with advantages of intralesional methotrexate over 5 - FU including decreased number of injections decreased pain and lower cost.

Recently, there are a few reports of successful treatment of solitary KA by applying 5% imiquimod cream a member of the imidazoquinoline family of drugs, commercially available as Aldara, as a topical immunomodulator in the group of toll-like receptor 7 and 8 agonists. Imiquimod has a therapeutic role as an antiviral and antitumour drug.

Most patients applied the cream 3 times a week for 5 to 7 months. Four to 11 weeks of application were required for the treatment, and sometimes adverse effects which depended on the inflammation resulting from the immunological reaction, such as burning sensation, itching, bleeding, stinging sensation, pain, erythema and erosions occurred. Other side effects include upper respiratory tract infection, sinusitis, and headache. Pregnant women should use imiquimod only if the potential benefits outweigh the risks. Clinicians should also be aware of pigmentation changes in patients [14].

The severity of side-effect is dose-dependent. In spite of these inconveniences, KA can be successfully treated with topical imiquimod, because of lower invasiveness and non-inferiority in the functional or cosmetic outcome.

In previously reported cases of keratoacanthoma treated with imiquimod cream, the average duration to obvious improvement was 5.0 ± 1.8 weeks, and that to complete remission was 7.4 ± 2.2 weeks [8].

In a report of two cases of KA-treated with imiquimod 5% cream in which the cream was applied daily for the first 6 or 7 days, and then reduced to alternate days according to the tolerance and erythema severity of the patient, the results show that frequent application of imiquimod at the initial treatment induces a prompt regression of KA and in both patients, the tumours fully regressed after five weeks of treatment [15].

However, the analysis of previously reported cases showed no statistically significant difference in the duration to remission between cases applied once per day (median: 6.5 weeks; range of 5 to 8 weeks) and less than once per day (median: 6 weeks; range of 4 to 11 weeks). Similarly, the duration to complete remission was not related to age, size and the duration of KA.

In a previously reported analysis of 18 cases the medians of the duration to complete remission was 6 weeks in 14 previously reported cases (range of 4 to 11 weeks), and 10 weeks in another 4 cases (range of 9 to 11 weeks) [8].

Mature KA undergoes regression in 6 weeks, and topical imiquimod can promote the regression of KAs [16].

In 18 - year retrospective study on the outcomes of keratoacanthomas with different treatment modalities the median duration to resolution was 6 months for intralesional, oral or topical medications [17].

Also suggests that lesions treated with imiquimod cream should be considered for biopsy to judge histopathological remission after 5 to 8 weeks of application to shorten the duration of the treatment [8].

In cases of solitary KAs after rapid proliferation, a mature KA undergoes regression in 4 to 6 weeks, leaving an atrophic and hypopigmented scar. This process from proliferation to regression usually takes about 4 to 9 months, but there are some persistent cases which take more than one year [8] [4].

Claims that spontaneously resolved keratoacanthomas leave poor quality scars that may need surgical revision were not confirmed in the illustrated series of 19 patients with solitary KAs which is the largest published to date [13].

There are contrasting opinions on cosmetic outcomes with spontaneous resolution of the KA versus therapeutic intervention. Treatment minimises scarring which helps better cosmetic results. Therefore, treatment is recommended in most cases. Some authors advocate surgical excision to result in a superior cosmetic outcome in comparison to lesions observed for spontaneous regression [4].

Failure of treatment with any of these medications is indicated by a further progression of the lesion associated with pain. This may signal an underlying aggressive SCC in clinically classic large KAs.In these cases, complete surgical excision of the lesion with histologic evaluation is recommended.

In conclusion, the results from our case report demonstrate that topical imiquimod can be an effective treatment option for solitary KAs when present in cosmetically sensitive areas. During treatment, the patient experienced only mild stinging sensation at the site of application.

The choice of imiquimod as a therapeutic modality was based on patient's age, lesion size and location, medication availability and the patient's reluctance to receive intralesional injections.

In our case, the outcome of the topical treatment with imiquimod was cosmetically and functionally superior to complete surgical excision.

Treatment of keratoacanthoma (KA) is primarily surgical. Medical treatment should be reserved for exceptional cases where surgical intervention is either not feasible or desirable. For example, medical intervention may be appropriate in patients with multiple lesions, in lesions not amenable to surgery because of size or location, and in patients with comorbidities that dissuade surgical procedure.

Most of the literature concerning medical intervention for keratoacanthoma is limited to case reports or case series. Be cautious when deciding to pursue medicine instead of surgical intervention and perform appropriate follow-up.

Failure to treat keratoacanthoma appropriately may result in local destruction, unacceptably high levels of recurrence and metastasis, or in other cases, may result in an unfavourable risk-to-benefit ratio.

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Case Report

Surgical Management of Facial Features of Robinow Syndrome: A Case Report

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Keywords: Robinow Syndrome; Genetic disorder; Zygomatic Augmentation; Closed Rhinoplasty

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Abstract

BACKGROUND: Robinow Syndrome is an extremely rare genetic disorder characterised by abnormalities in head, face and external genitalia. This disorder exists in dominant pattern with moderate symptoms and recessive pattern with more physical and skeletal abnormalities. It was first introduced by Menihard Robinow in 1969. It was related to chromosome 9q22 ROR2 gene related to bone and cartilage growth aspects.

CASE PRESENTATION: A 17-year-old Egyptian male presented to National Research Centre Orodental genetics Clinic with typical features of short stature and facial dysmorphism weighted 50 Kg and measured 150 cm height complaining of facial disfigurement. There was no significant prenatal history, and family history was negative for congenital disabilities and genetic disorders. Clinical examination revealed macrocephaly and special facial features as prominent forehead, deformed ear pinna, hypertelorism, flat nasal tongue tie, deficient malar bone, bow-shaped upper and lower lips and dimpled chin. Orally the patient suffered from tonetie, gingival hypertrophy and dental malalignment. The orthopantomogram showed multiple impacted teeth. The physical examination revealed that the patient had deformed spine, short limbs with ectrodactyly, micropenis & hypospadias. Surgical management included correction of midface deficiency with zygomatic augmentation, closed rhinoplasty for the broad nose, lips muscles release and tongue tie relief. The patient is currently undergoing orthodontic treatment for his teeth.

CONCLUSION: Improvement of facial features and a good psychological impact on the patient and his family.

Introduction

Robinow syndrome is an extremely rare genetic disorder characterised by abnormalities in the head, face, stature, extremities and external genitalia. This disorder exists in dominant pattern with moderate symptoms and the recessive pattern with more physical and skeletal abnormalities.

Robinow Syndrome was first introduced by Menihard Robinow in 1969 [1]. It was related to a gene on chromosome 9q22. Tyrosine Kinase-like orphan receptor 2 ROR2 gene was related to bone and cartilage growth aspects [2].

Case presentation

A 17 year - old Egyptian male, born of unrelated parents had presented to National Research Center Orodental Genetics clinic with short stature, and facial dysmorphism weighted 50 Kg and measured 150 cm height complaining from facial disfigurement. There was no significant prenatal history, and family history was negative for any previous congenital disabilities or genetic abnormalities. Clinical examination revealed macrocephaly and special facial features as the prominent forehead, deformed ear pinna, hypertelorism, flat nasal bridge, deficient malar bone, bow-shaped upper and lower lips (Figure 1).

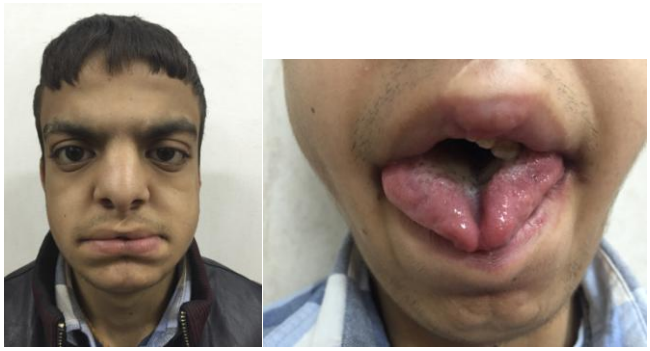


Figure 1: Facial features of Robinow syndrome (left); Abnormal tongue (right)

Orally the patient suffered from tongue tie (Fig. 1right), dental malalignment (Fig. 2a) and gum hypertrophy (Fig. 2b).

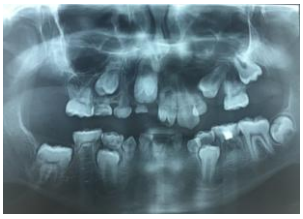
a)  b) 

Figure 2: a) Panoramic X-ray showing dental crowding; b) Gum hypertrophy

The orthopantogram showed multiple impacted teeth. General physical examination revealed that the patient had deformed spine, short limbs with ectrodactyly (Fig. 3), micropenis and hypospadias.

Figure 3: Ectrodactyly

Surgical Management

Soft tissue surgical repair was made for this patient to correct lip muscles (upper & lower) deficiency in midline resembling whistle deformity in bilateral cleft lip cases, with dissection of orbicularis oris muscle fibers intraorally using VY technique to increase the mucosal tissue with plication suture in order to have muscle continuity & approximation of levator labii superioris fibers.

Lip surgery included V-Y incisions on the mucosal surface of the upper & lower lips. Through this approach, the two lateral bulges of the orbicularis muscle were reached, dissected and repositioned with a more medial position using 3 0 vicryl sutures to compensate for midline muscle bulk deficiency.

In the upper lip, the levator labii superioris was reached on both sides and approximated together and suspended to ANS periosteum to achieve lengthening and eversion of the lip. The V incision was closed in Y technique to help in formation of lip tubercle.

As regards the lower lip V - Y technique was inverted to help in increasing the height of mucosal surface and decreasing the eversion of the lip laterally through excision of the excess mucosa towards the midline and suturing it medially. The accentuated labiomental groove was improved just following the lower lip surgery (Figure 4 a, b).

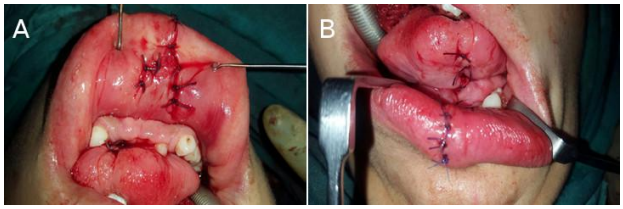


Figure 4: a) Upper lip surgery; b) Lower lip surgery

Closed surgical rhinoplasty was performed for the nasal bridge to correct the broad nose. The surgical approach to the nose was reached through a bilateral marginal incision. Reductive tip plasty was performed through resection of small tip of the cephalic part of the lower bilateral cartilages and applying an interdorsal suture to refine the tip and intercrural sutures to approximate the medial crura. Two lateral para medial osteotomies together with two lateral osteotomies were done to narrow the wide bony pyramids.

The patient had to wear a gypsum surgical stent over the nose with plasters for almost a month till complete healing and some oedema was clinically noticed that was treated afterwards with anti-inflammatory and took some time to subside (Figure 5a, 5b).

Zygomatic bone augmentation was made by harvesting autogenous cortical cancellous bone block from the chin intraorally via vestibular incision about 1 cm^2 to correct midface depression bilaterally. This technique was preferred over using alloplastic graft material to avoid tissue interaction or the possibility of body rejection (Figure 5c, 5d).There was a noticeable improvement in the facial features and profile appearance as well as the positive psychological impact (Figure 6, 7 and 8). The patient is currently

undergoing orthodontic treatment for dental arch continuity.

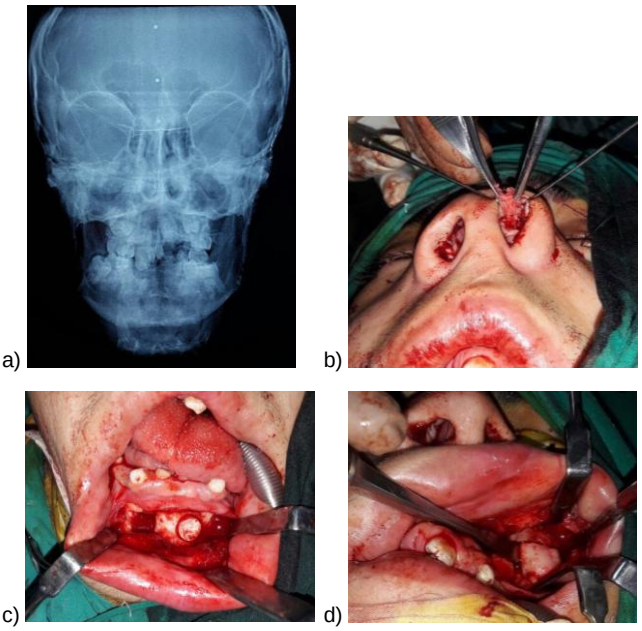


Figure 5: a) PA radiographic view; b) Closed surgical rhinoplasty; c) Harvesting chin bone; d) Zygomatic augmentation

Discussion

Robinow Syndrome is an extremely rare genetic disorder characterised by short stature, fetal face, abnormalities in the head, and external genitalia, as well as vertebral segmentation. It was introduced by Menihard Robinow in 1969 [1].

Figure 6: a) Lip before surgery; b) Lip after surgery

Based on the initial pedigree, this syndrome was attributed to be an autosomal dominant inherited syndrome [Online Mendelian Inheritance in Man (OMIM) 180700] with high penetrance [1] [2]. Researchers linked the gene for the autosomal recessive Robinow syndrome to chromosome 9q22. The gene is responsible for cartilage and bone growth [3]. The male to female ratio of patients with Robinow syndrome is 1:1. Although the incidence is about 1:500,000, however, the prevalence is slightly less due to the death of 5 - 10 % of patients during infancy [4].

Two forms of the disorder exist the dominant & recessive form which occurs more common. Patients with the dominant form often suffer from moderate symptoms [5]. While patients with a recessive form that is more aggressive, are usually more physically affected, and individuals may exhibit severe skeletal abnormalities particularly in Turkey, Oman & Czechoslovakia [6] [7].

Figure 7: a) Face Before; b) Face after surgery

In 2002 a case of 10 years male patient was presented by Holsakar HS et al. [8] born of unrelated parents after a normal pregnancy, presented with facial dysmorphism and short stature.

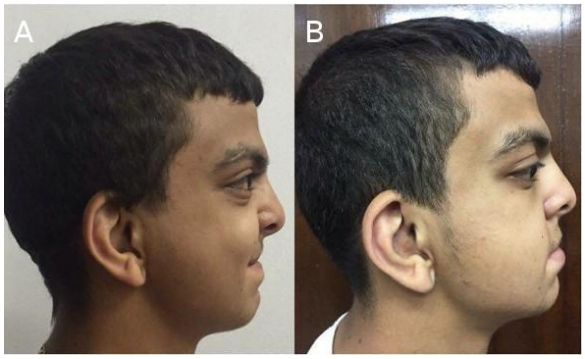


Figure 8: a) Profile before; b) Profile after surgery

There was no significant peri-natal history, and family history was negative for congenital disabilities and genetic disorders. The patient who was 6 months old weighed 43 Kg, measured 54 cm height and head circumference 36 cm. Management includes orthodontic treatment for dental malalignment and facial reconstruction in selected cases also surgical repair of vertebral deformity and growth hormone therapy occasionally.

In the present case, we did some facial reconstruction including nose, lips and midface using autogenous bone block harvested from the chin rather than using alloplastic graft material as polycaprolactone PCL for fear of tissue interaction and the possibility of graft rejection. In 2009 an 8 years old female patient was reported by Eronat N. et al. [9]. The patient was born to consanguineous parents and

had typical recessive type anomalies such as short stature & dysmorphic facial features, besides the typical orodental findings. No surgical interference was made for that case. However, In the current study, the decision was made for surgical management concerning the facial features trying to convert the looks of the patient from syndromic to non-syndromic look.

After the soft tissue surgery reconstruction especially for the nose using closed rhinoplasty with no extra nasal scars for removal of the nasal hump and zygomatic augmentation, the patient looked different. In 2008 Grothe R et al. [10] introduced an interesting case of Robinow with severe hyperplastic gingival tissue impeding both normal tooth eruption as well as orthodontic movement. Growth hormone GH therapy has been proved to cause improvement in the growth rate in children with Robinow syndrome and GH deficiency.

The prognosis for Robinow syndrome is good with more than 80% of patients having normal intelligence [11] [12]. A fetal ultrasound can provide a parental diagnosis at 19 weeks of pregnancy. However, it's not always easy to differentiate between a fetus suffering from the milder dominant form from the serious recessive form. Radiographs are useful for assessment of rib or spinal deformities anomalies and may also help to document face and hand anomalies [13]. The patient still needs further plastic surgery for ears and digits. Also, there is still undergoing orthodontic treatment for teeth malalignment correction.

In conclusion, improvement of facial features as well as the psychological impact on the patient and his family.

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Case Report

Ovarian Strumal Carcinoid Tumour: Case Report

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Keywords: Ovarian teratoma; Strumal carcinoid; Carcinoid syndrome

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Abstract

BACKGROUND: Ovarian strumal carcinoid is a germ cell tumour characterised by a mixture of thyroid tissue and carcinoid. Ovarian struma is a very rare occurrence with 0.3-1% incidence of all ovarian tumours and 3% of mature teratomas. Primary carcinoid ovarian tumours are still uncommon as a part of mature teratoma or mucinous cystadenoma. There are four major variants of a carcinoid tumour: insular, trabecular, strumal and mucinous. A strumal carcinoid is an unusual form of ovarian teratoma composed of an intimate admixture of thyroid/carcinoid tissues.

CASE REPORT: This is a case report of a 59-year old woman with a 5-year clinical history of perimenopausal uterine bleeding and three explorative curettages. Gynaecological and ultrasound examinations revealed ovarian enlargement with a diameter of 50 mm with hypoechoic zones suspected of benign teratoma. The diagnostic test such as Ca-125, AFP, free-T4 and TSH was in normal range. A smooth, solid right ovarian 50 an mm-size tumour, as well as small amount of fluid in the Douglas pouch, was found during the total abdominal hysterectomy, bilateral salpingo-oophorectomy and staging biopsy. The histopathology revealed teratoma with strumal carcinoid tumour IA stage according to AJCC 2010 of the right ovary and negative cytopathology of the fluid from the Douglas pouch. On the postoperative 2-year control, the patient was tumour free, and Ca-125, free-T4 and TSH were in normal range.

CONCLUSION: We would like to point out those specific diagnostic tools, such as ultrasound and Ca-125 have low specificity and sensitivity in detection of this rare ovarian malignancy.

Introduction

Ovarian strumal carcinoid belongs to the germ cell family of ovarian malignancy, which is an intimate admixture of normal thyroid tissue and carcinoid. Ovarian struma has a very rare occurrence with 0.3 - 1% incidence of all ovarian tumours and 3% of mature teratomas. Primary carcinoid tumours of the ovary are uncommon, rarer than struma ovarii and account only for 5% of ovarian teratomas. Three - fifths of the strumal carcinoids arise in dermoid cysts or mature, solid teratomas. They are frequently composed of mature cystic teratomas or, less commonly, mucinous cystadenomas. Most patients with strumal carcinoid have no symptoms of carcinoid syndrome like flushing and diarrhoea, but only symptoms of enlarging mass. They can also be just incidental findings. According to histopathology, there is four major variants of carcinoids: insular, trabecular, strumal and mucinous. Treatment with a simple oophorectomy or salpingo-oophorectomy is effective. Ovarian strumal carcinoid metastasises occasionally, and such a type of neoplasm should be treated as an ovarian tumour with low malignancy potential.

We present a patient with ovarian teratoma and strumal carcinoid tumour.

Case Report

A 59 - year old postmenopausal woman was referred to our hospital without any symptoms at the regular gynaecological checkup, which revealed an enlarged cystic right adnexal tumour with mixed

echogenicity and increased blood flow. In the perimenopausal period, she had 3 consecutive explorative curettages for excessive bleeding, and the histopathological analysis revealed normal, benign findings. Her menopause occurred at the age of 54, and after that, she never had any vaginal bleeding.

She was admitted to our gynaecological department for accurate diagnosis and adequate treatment. Pelvic examinations revealed an enlarged right ovary whose dimensions were inappropriate for the woman's age, with a diameter of 43 mm with both hypoechoic and hyperechoic zones. There was no amount of fluid in the Douglas pouch. The uterus was in AVFL and had a thin endometrial lining with no other notable features observed. The risk of ovarian malignancy index (ROMI) = 9, i.e. there is a low risk for malignancy: cystic structure with < 1/4 solid parts (1point) + senium (1 point) + multilocularity (2 points) + opalescent intralocular liquid (2 points) + intralocular papillary vegetation of 3 - 5mm thickness (1 point) + thickness of the capsule of 3 - 5mm (1 point) + clear rugged margin (1 point) [1].

Figure 1: Ultrasound examination which revealed a cystic structure with < 1/4 solid parts, opalescent intralocular liquid, intralocular papillary vegetation of 3 – 5 mm thickness, the thickness of the capsule of 3 – 5 mm and a clear, rugged margin

The results of urinalysis and blood chemistry tests were within normal ranges and Ca125 - 11.4 U/mL. Routine investigations including serum electrolytes and thyroid function test were all within normal limits. Serum tumour markers, such as Ca125, carcinoembryonic antigen and Alpha-fetoprotein (AFP) were within normal limits. According to the clinical and imaging information and postmenopausal status of the patient, the possibility of a cystic ovarian teratoma was considered and, after discussion with the patient and her family, exploratory laparotomy was planned.

The patient underwent surgical treatment, total abdominal hysterectomy with bilateral salpingo-oophorectomy, along with omentectomy, peritoneal washing and peritoneal sampling biopsy. During the procedure, a cystic tumour with a diameter of 5 cm - size arising from the right ovary with the intact capsule, mobile and well circumscribed was visualised. The uterus left ovary, and both tubes were normal. At the same time, a peritoneal washing was performed for cytological examination. The postoperative period was uneventful, and the patient was discharged on the 7th postoperative day.

According to the pathology report, the tumour of the right ovary measured 6 x 4.5 x 4.5 cm, and it was lobulated, with the smooth outer surface. The cut surface revealed a cystic formation filled with sebaceous material and a tuft of hair. In the wall of the cyst, there was solid, homogenous, tan - brown to yellow, circumscribed nodule measured 3.5 cm.

Microscopic examination revealed a cyst lined by stratified squamous epithelium with skin appendages, together with mature neuronal elements and fat tissue (Figure 2A). The solid nodule was composed partly of thyroid tissue with thyroid follicles filled with colloid and partly of tumour cell clusters composed of monomorphic cells with abundant granular cytoplasm. The nuclear chromatin was finely granular and "salt and pepper" in appearance. The tumour cells were arranged in trabecular structures, or in solid nests and small acini (Figure 2B, and 3).

A) B)

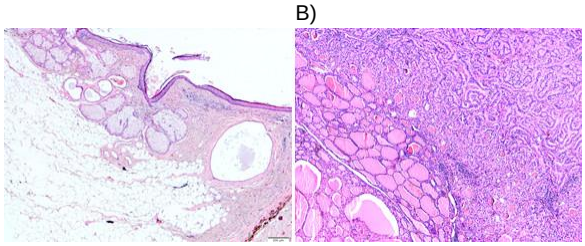

Figure 2: A - Mature cystic teratoma: stratified squamous epithelium with skin appendages, mature neuronal elements and fat tissue, H&E x10; B – Hematoxylin-eosin staining of the strumal carcinoid tumour; Thyroid tissue (bottom left) and carcinoid tumour (upper right), H&E x10

Immunohistochemically, tumour cells were diffusely positive for synaptophysin, neuron-specific enolase (NSE) and CD56 and focally positive for chromogranin A. Mitotic activity of tumour cells was 3 mitoses/10HPF and proliferative index measured with Ki - 67 was 10% (Figure 4).

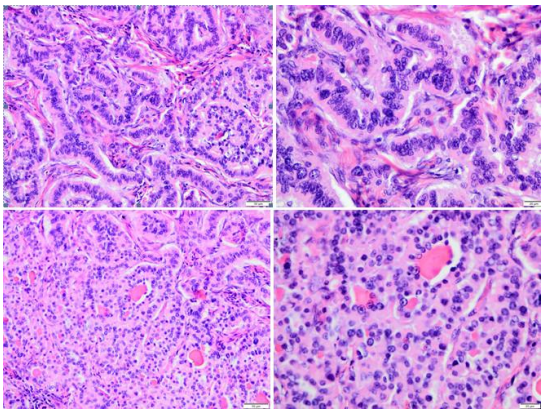

Figure 3: Trabecular carcinoid tumour composed of solid parts and showing a trabecular growth pattern (H&E × 20) (left up). Carcinoid cells with oblong nuclei and columnar cytoplasm presented with long, wavy, parallel ribbon-like arrangement (H&E × 40) (right up). Insular carcinoid tumour composed of solid nests and small acini (H&E x 20) (left down); H&E x 40 (right down)

This part of the tumor was diagnosed as trabecular and insular carcinoid. Because of the presence of mature cystic teratoma and thyroid components, the definitive diagnosis was mature cystic teratoma with strumal carcinoid. Cytological examination of the fluid from the Douglas pouch was negative for tumour cells.

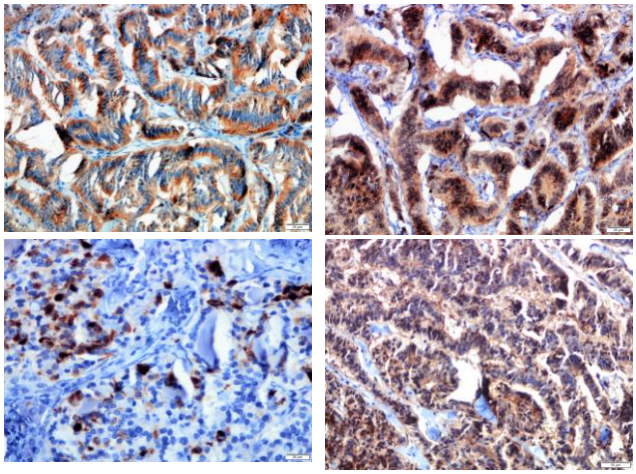

Figure 4: Immunohistochemically tumor cells were positive for: synptophysin, x40 (left up); NSE, x 40 right up); chromogranin A, x 40 (left down); CD56, x 20 (right down).Figure 4. Immunohistochemically tumor cells were positive for: synptophysin, x 40 (left up); NSE, x 40 right up); chromogranin A, x 40 (left down); CD56, x 20 (right down)

According to UICC and AJCC 7th edition from 2010, the disease was in IA stage. Given her pathological findings, she was referred to an oncologist for consultation but will have a good prognosis, and she is scheduled to be followed up by physical examinations, tumour markers ultrasounds, and CT scans.

Discussion

Adnexal masses are the most common gynaecological findings. Ovarian tumours, as a part of adnexal tumour masses, represent two - thirds of these cases. Histopathological diagnosis after adequate surgical treatment is the golden standard for a final diagnosis of an adnexal mass. The primary ovarian carcinoid tumours are rare and represent less than 0.1% of ovarian malignancies [2].

According to the WHO classification, they represent a group of ovarian monodermal teratomas [3]. Monodermal teratoma is a benign teratoma composed either solely or predominantly of only one highly specialised tissue type. Those composed predominantly of thyroid tissue are termed struma ovarii [4]. Most tumours present in peri - or postmenopausal women with symptoms of enlarging mass or are just incidental findings [5]. They most commonly appear as a unilateral mass, but in one - fifth of the cases a contralateral tumour can also be found. More than a half of ovarian carcinoids are found as a part of mature cystic teratoma. Regarding the clinical signs and symptoms, some patients present with typical signs and symptoms of the carcinoid syndrome such as episodic cutaneous flushing, abdominal cramps, diarrhoea, carcinoid heart disease, etc. mediated by bioactive substances that carcinoid tumour cells produce [2]. Carcinoid tumours secrete a wide variety of neurohumoral substances such as serotonin, histamine, tachykinin, bradykinin, kallikrein, corticotrophin, substance P, motilin, and prostaglandins [6]. The above - mentioned complications are almost solely due to the secretion of serotonin. In our case, the patient had no symptoms of carcinoid syndrome, nor symptoms due to the enlarging mass.

Primary ovarian carcinoids are histologically divided into four major types: insular, trabecular, strumal and mucinous. A mixed type has also been reported, which is composed of any combination of the pure types. Primary ovarian carcinoids also arise in association with mature cystic teratomas or mucinous tumours and present various findings on preoperative images. Therefore, the preoperative diagnosis of these tumours may be difficult [7]. Islands of uniform neoplastic cells are typical for insular carcinoids. About 30% of these tumours are associated with the carcinoid syndrome. Trabecular carcinoids are characterised by the growth of tumour cells in trabeculae and only rarely present with endocrine manifestations [2]. Mucinous carcinoid tumours of the ovary are pure tumours, and rarely represent part of the strumal carcinoid. It is considered that primary mucinous carcinoid tumour of the ovary represents a specific histopathologic entity. Unlike other types of primary ovarian carcinoid tumours, it behaves like an aggressive malignant neoplasm [8]. Nevertheless, multiple metastases with a higher mitotic rate and focal necrosis have been reported. The presence of mitoses or necroses in a tumour is useful for predicting poor prognosis.

Differential diagnoses of primary ovarian carcinoid include metastatic carcinoid, granulosa cell tumours, poorly differentiated primary or metastatic adenocarcinoma, Brenner tumours and androblastoma [2] [13]. Approximately 5% of primary carcinoid tumours of the non-mucinous type have a malignant clinical course, but so far there are no histological parameters that can predict malignancy [2] [9]. Insular carcinoids are among the tumours with low malignant potential. Cases of strumal carcinoid metastases which consist of both the carcinoid and thyroidal type are rarely reported [9]. Mucinous carcinoids tend to be more aggressive in the clinical course.

Premenopausal women with tumours confined to the ovary may be treated with fertility-sparing surgery, as tumors are usually unilateral and

carry a good prognosis, but careful staging to exclude occult metastases is important. However, in the absence of controlled trials to validate this approach, hysterectomy with bilateral salpingo - oophrectomy and surgical debulking of extra-ovarian spread and/or metastases is the treatment of choice [10] [11]. In rare patients with a mucinous variant of the ovarian carcinoid, omentectomy and para - aortic lymph node dissection may also be needed because these tumors spread mainly through lymphatics [10] [12].

However, because of the difficulty of setting an accurate preoperative diagnosis, most cases have been diagnosed based on postoperative pathology findings.

With this case report the correlation between the preoperative clinical assessment and intraoperative assessment and the histopathological diagnosis can be made.

We would like to point out that specific diagnostic tools, as well as serological tests for ovarian malignancy, have low specificity and sensitivity in detection of this rare ovarian malignancy with no clinical symptoms.

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Case Report

Rathke's Cleft Cyst or Pituitary Apoplexy: A Case Report and Literature Review

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Keywords: Rathke Cleft Cyst; Apoplexy; MRI; T1-weighted

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Abstract

BACKGROUND: During the examination of the sellar region by magnetic resonance imaging, hyperintensity in T1 weighted is a common finding. This signal intensity has different sources, and its significance depends on the clinical context. Pathologic variations in T1 signal hyperintensity may be related to clotting of blood (pituitary apoplexy) or the presence of a high concentration of protein (Rathke cleft cyst). The purpose of this study is to describe the significance of intracystic nodule, a diagnostic characteristic found in Rathke's cleft cyst, on MRI.

CASE REPORT: We will present the case of a 20–year-old girl which referral to our hospital for head examination with magnetic resonance imaging because she has a post-traumatic headache. Pathological findings presented in T1-weighted hyperintensity intrasellar which persist even in T1 weighted-Fat suppression. These changes signal the presence of methemoglobin imposes. The patient is a referral to laboratory tests which result in rate except for slight value increase of prolactin. Recommended controller examination after a month but finding the same results which exclude the presence of methemoglobin.

CONCLUSION: Morphological characteristics and signal intensity can impose the presence of high concentration of protein (Rathke cleft cyst).

Introduction

Rathke cleft cysts (RCC's) are benign lesions that typically arise within the sella between the anterior and posterior lobes of the pituitary [1]. In 1913 the Goldzieher described the first case of RCC as an incidental postmortem finding. The description of RCC has expanded since the advent of computed tomography (CT) scanning and magnetic resonance imaging (MRI), showing that the incidence of this disease which discovery was only by autopsy was underestimated. Most often asymptomatic, RCCs have been found incidentally in 4% to 33% of autopsies [2] [3] [4] [5]. These lesions, however, can cause mass effect on surrounding structures such as the pituitary gland and optic chiasm, leading to a headache, pituitary dysfunction, or visual disturbance [6] [7] [8]. The epithelium is often ciliary and may contain bowl-shaped cells. The content of a cyst is usually mucous, and less frequently, it is filled with exudates or remnants of exfoliated cells. Rathke cleft cysts are remnants of the Rathke pouch, a structure of ectodermic origin formed during the fourth week of gestation. The Rathke pouch extends caudally to fuse with the infundibulum around the eighth week of gestation, forming the craniopharyngeal duct. The Rathke pouch then leads to the formation of the adenohypophysis and pars intermedia while the infundibulum generates the neurohypophysis. During this time, the Rathke cleft is formed in the region of the pars intermedia. Failure of this cleft to regress during further development can lead to cystic dilation and the formation of an RCC [1] [2] [3] [4] [5] [6]. Larger RCCs can extend upward into the suprasellar region, and comparisons of symptomatic and asymptomatic lesions have suggested that large

size and suprasellar extension of RCCs may be associated with a greater tendency toward symptomatic presentation [9] [10]. Although most RCCs originate in the sella, there have been reports of purely suprasellar RCCs. Calcifications of the cyst walls are rarely observed. Although asymptomatic RCCs can safely be followed up with serial imaging, the standard treatment for symptomatic RCCs is surgical decompression, typically through a transsphenoidal approach.

Symptomatic patients have RCCs usually manifest headaches. One such case is reported. The author also reviews published reports on RCCs presented like apoplexy and described radiological characteristics of this rare entity.

This work aims to emphasise the value of MRI in the positive and differential diagnosis of this disease through a case of Rathke's cleft cyst with a literature review.

Case Report

We are presenting the case of a 20 – year - old girl, on referral to our hospital for head examination with magnetic resonance imaging because she has a post-traumatic headache. The patient was cooperative but slightly confused. Neurological examination revealed no focal deficit including oculomotor palsy or visual field defect, and there was no evidence of neck stiffness

The patient underwent magnetic resonance (MR) imaging of the sella with and without contrast injection. Pathological findings presented heterogeneous signal intensity in T2 - weighted and T1 - weighted hyperintensity intrasellar pituitary which persists even in T1 weighted - Fat suppression. The lesion is with an anteroposterior diameter (AP) 7 mm and craniocaudal (CC) 9 mm which is located at the posterior part of the adenohypophysis (Figure 1), while the pituitary gland has dimensions in AP diameter 13 mm and CC diameter 10 mm. There are no signs of compression on the chiasma opticum although it arrives very close.

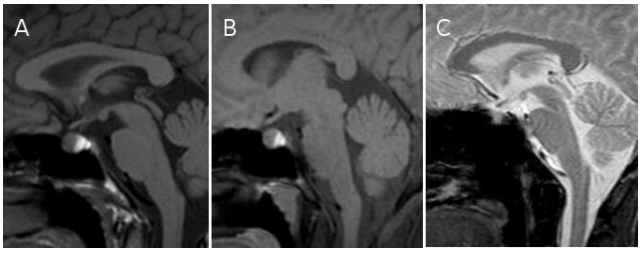

*Figure 1: The first examination, magnetic resonance images of a patient presented: The lesion is isointense with hyperintensity on T1 - weighted images and T1 weighted - Fat suppression (A and B). Heterogeneous signal intensity on the T2*weighted image (C)*

This increased signal intensity has different sources and is given importance when interpreting the depending on the clinic of imaging findings.

These findings suggested the presence of haemorrhage in a pituitary adenoma, the presence of methemoglobin impose. The patient is a referral to laboratory tests which result in rate except for slight value increase of prolactin (35 ng/ml), and we recommended controller examination after a month but finding the same results which exclude the presence of methemoglobin. Morphological characteristics and signal intensity to impose the presence of high concentration of protein (Rathke cleft cyst) (Figure 2).

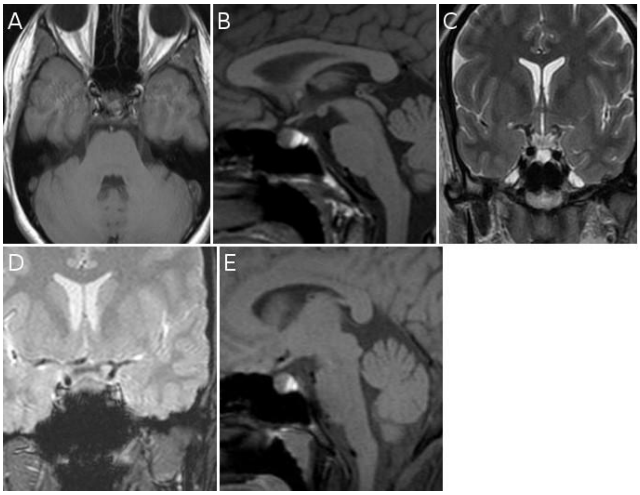

*Figure 2: The first examination, magnetic resonance images of a patient presented: The lesion is isointense with hyperintensity on T1 - weighted images axial (A) and sagittal (B), hyperintensity in T1 weighted- Fat suppression (E) and T2 - weighted image (C), while heterogeneous signal intensity on T2*weighted image (D)*

Discussion

Rathke's cleft cysts (RCC) are well - delineated structures that vary in size from several millimetres to 1 – 2 cm. They are found in less than 1% of primary brain tumours. In most cases, RCC is small, asymptomatic mass lesions located in the intrasellar or the intrasuprasellar space [9]. RCC may be seen at any age; however, they are more frequent in adults.

In 1913, Goldzieher described the first case of RCC as an incidental postmortem finding. Rathke cleft cysts are thought to be non - obliterated remnants of the primitive craniopharyngeal duct, which is a part of the Rathke pouch. In the superoinferior plane, RCCs are usually located entirely within the sella or contain both intrasellar and suprasellar components. In the anterior-posterior plane, RCCs typically reside between the pars

anterior and pars intermedia of the pituitary gland. Purely suprasellar RCCs situated above a normal sella are rare. The Rathke pouch gives rise to the pars distalis (anterior lobe) and pars intermedia (intermediate lobe) in the sella, as well as the pars tuberalis, a structure that resides above the anterior lobe and the diaphragm sella in the suprasellar cistern. It is therefore thought that purely suprasellar RCCs arise from a remnant of the Rathke pouch within the pars tuberalis in the suprasellar cistern [11] [12] [13].

MRI is the modality of choice for the detection of RCCs [14]. Thin - section sagittal and coronal MRI scans should be obtained through the sella. MRI is superior to CT scanning for evaluating RCC mass extension. Sagittal and coronal MRI scans provide reliable information concerning the relationship of the mass to the optic nerves, optic chiasma and hypothalamus. Coronal MRI is also helpful in the evaluation of the lateral extension of the sellar cyst and its relationship to the internal carotid arteries and cavernous sinuses. MRI also has superior multiplane capabilities and contrast resolution compared with those of CT scanning. The advantage of CT scanning is that it is superior to MRI in depicting small amounts of calcium. This advantage can be important because the presence of calcification tends to indicate an alternative diagnosis, such as craniopharyngioma, although small calcifications are observed in some cases of RCC [15].

CT scanning is also superior to MRI in the evaluation of associated bony remodelling and in depicting small amounts of calcium. Coronal MRI is also helpful in the evaluation of the lateral extension of the sellar cyst and its relationship to the internal carotid arteries and cavernous sinuses. MRI also has superior multi- plane capabilities and contrast resolution compared with those of CT scanning.

The best imaging clue is a non - enhancing non - calcified intrasellar and/or suprasellar cyst with an intracystic nodule. While this is the typical picture, the imaging characteristics vary widely.

Approximately half are hyperintense on T1WI, while half are hypointense. On T2WI, 70% are hyperintense, and 30% are isointense or hypointense. Although no characteristic MRI features have been identified, many RCCs are in one of the following two groups:

RCC’s with low signal intensity on T1WI and high signal intensity on T2WI. RCC’s with high signal intensity on T1WI and variable signal intensity on T2WI.

The cystic contents of the first group resemble those of cerebrospinal fluid (CSF). In the second group, an increase in the signal on T1WI has been related to the high content of mucopolysaccharides, which is believed to result from an increase in the number of mucin-secreting cells in the cyst wall, as well as from an increase in the activity of these cells. Rathke cleft cysts do not enhance after contrast material administration, although an enhancing rim of the displaced compressed pituitary gland is present in approximately half of the cases [16].

Forty percentages of RCCs are intrasellar, and 60% are a suprasellar stretch, while rarer are cases with complete suprasellar stretch. Our case is an intrasellar stretch (type I).

The most common approach in the treatment of RCCs is transsphenoidal surgery, in which the cyst is partially excised and drained [17].

The purpose of this study is to describe the significance of intracystic nodule, a diagnostic characteristic found in Rathke's cleft cyst, on MRI

In conclusion, authors report a rare case of asymptomatic RCC which was presented with hyperintensity in T1 – weight, like pituitary apoplexy. It is hard to differentiate Rathke Cleft Cysts apoplexy from RCCs with hight protein concentration based only MRI image. RCCs should be considered if a patient has symptoms of apoplexy. The MRI is effective in the positive and especially the differential diagnosis of these cysts, and to guide the therapeutic decision. Once the diagnosis is considered, a spaced clinical and MRI monitoring is adopted in cases of the asymptomatic cyst, while a surgical treatment is proposed for the rare symptomatic cysts.

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Dental Science

Effect of Luting Cements On the Bond Strength to Turkom-Cera All-Ceramic Material

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Keywords: Shear bond strength; Luting cement; All – ceramic; Adhesion

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Abstract

BACKGROUND: The selection of the appropriate luting cement is a key factor for achieving a strong bond between prepared teeth and dental restorations.

AIM: To evaluate the shear bond strength of Zinc phosphate cement Elite, glass ionomer cement Fuji I, resin-modified glass ionomer cement Fuji Plus and resin luting cement Panavia-F to Turkom-Cera all-ceramic material.

MATERIALS AND METHODS: Turkom-Cera was used to form discs 10mm in diameter and 3 mm in thickness (n = 40). The ceramic discs were wet ground, air - particle abraded with 50 - μm aluminium oxide particles and randomly divided into four groups (n = 10). The luting cement was bonded to Turkom-Cera discs as per manufacturer instructions. The shear bond strengths were determined using the universal testing machine at a crosshead speed of 0.5 mm/min. The data were analysed using the tests One Way ANOVA, the nonparametric Kruskal - Wallis test and Mann - Whitney Post hoc test.

RESULTS: The shear bond strength of the Elite, Fuji I, Fuji Plus and Panavia F groups were: 0.92 ± 0.42, 2.04 ± 0.78, 4.37 ± 1.18, and 16.42 ± 3.38 MPa, respectively. There was the statistically significant difference between the four luting cement tested ($p < 0.05$).

CONCLUSION: the phosphate-containing resin cement Panavia-F exhibited shear bond strength value significantly higher than all materials tested.

Introduction

The main purpose of the luting agent is to seal the gap at restoration-prepared tooth interface and retain the restoration in place to prevent its displacement during function [1].

Dental luting agent provides a connection between the indirect fixed restorations and the supporting prepared tooth structure [2]. The type of connection can be in the form of mechanical, chemical, micromechanical, or combination. These luting materials may be used for provisional or permanent cementation depending on their physical properties and planned longevity of fixed dental prosthesis [3] [4].

A strong and permanent bond between hard dental tissues and restorative materials provides improved marginal adaptation, thereby preventing microleakage resulting in pulpal sensitivity or penetration of bacteria and toxic substances and discolouration [5].

An adequate adhesion between ceramic and tooth substance is required for the successful function of ceramic restorations over the years [6]. Bond strengths are influenced by some factors one of which is the type of luting cement [7].

In vitro studies have documented the rationale for using conventional luting cement with the all-ceramic restorations including Turkom-Cera system

[5] [8] [9] [10]. Clinical trials on full - coverage high-strength ceramic restorations have also reported acceptable success rates with conventional luting agents [11] [12]. However, in the event of compromised retention or marginal seal, even high - strength ceramic crowns might benefit from adhesive bonding with a composite resin luting agent. Several in vitro and in vivo studies on this topic recommended adhesive cementation of ceramic and even high - strength ceramic restorations [4] [13] [14] [15] [16].

The integrity of the dental luting cement to ceramic surfaces plays an important role in the durability of the restorations; the failures originating from cementation surfaces acknowledged the need for a strong cement to improve the bonding at this critical area [17].

The bond strength of different luting agents to Turkom - Cera™ all - ceramic material has not been studied. Therefore, the objectives of this study were:

1. To determine the shear bond strength of Turkom - Cera luted with different types of cement.

2. To examine the association between shear bond strength and failure modes.

Materials and Methods

Materials used

Four types of luting agents were used; zinc phosphate cement (Elite, GC Corporation, Tokyo, Japan), glass ionomer cement (Fuji I, GC Corporation, Tokyo, Japan), resin-modified glass ionomer cement (Fuji Plus, GC Corporation, Tokyo, Japan) and resin luting cement (Panavia-F, Kuraray Medical Inc., Okayama, Japan) with its silane coupling agent. Also, forty Turkom - Cera (Turkom - Ceramic (M) Sdn Bhd, Puchong, Malaysia) discs 10 mm in diameter and 3 mm thick were prepared and used in this study.

Specimen preparation

Perspex split mould with five circular openings of 10 mm diameter and 3 mm thickness was used for the preparation of the Turkom - Cera disc specimens. A total of forty Turkom - Cera ceramic discs with 10 mm diameter and 3 mm thickness were prepared according to manufacturer instructions.

Each specimen was embedded in a die stone (Densite, Shufo, Japan) using plastic mould 30 mm in diameter and 30 mm high. The bonding surface of the specimens was at the same level of the embedding medium to form one flat surface.

After hardening for 24 hours at room temperature, the bonding surface of the specimens were sanded with a series of silicon carbide (SiC) abrasive papers in sequence (No. 400, 600, 800 and 1000 grit, Buehler) using a water - irrigated lapping machine (Metaserv® 2000, Buehler, UK) until the ceramic disc was perfectly flushed with the mounting mould and a flat surface was attained. All specimens were rinsed under running water and dried before bonding procedure. The ground bonding surface was examined under a microscope (Zoom Stereo EMZ - 1, MEIJI Techno Co., Ltd., Saitama, Japan) at 30x magnification to ensure that no abrasive particles were left on the surface.

Sample distribution and bonding procedure

According to the Four luting cement (Elite, Fuji I, Fuji Plus & Panavia F) used, four different groups were evaluated.

Group 1: Sandblasting + Zinc Phosphate cement.

Group 2: Sandblasting + Glass ionomer cement.

Group 3: Sandblasting + Resin-modified glass ionomer cement.

Group 4: Sandblasting + Resin cement.

Bonding procedure

All samples were mounted and secured on the shear bond test apparatus recommended by ISO/TS 11405/2003 [18] to bond a uniform amount of cement onto the Turkom-Cera bonding surface. The alignment apparatus consists of a holder for the specimen, a cylindrical split brass mould resulting in samples with a defined bond area of 3 mm diameter and 3 mm height, a silicone pad and an added load of 1 kg.

Sandblasting was performed with 50 - μm aluminium oxide (Al_2O_3) particles at an air pressure of 2.5 bars for 13 seconds from a distance of 10 mm. The discs were then steam cleaned and air dried. The brass split mould was carefully adapted to the bonding surface by raising the mounted specimen using the screw at the bottom of the mounted specimen. The split mould together with the mounted specimen was then quickly secured on to the bonding apparatus and tightly screwed. All cement were mixed according to manufacturer's instructions at room temperature (24°C). The cement were placed, using a plastic instrument, into the 3 mm diameter hole in the brass split mould while it was slightly raised to ensure a uniform flow onto the bonding surface and to avoid trapping of air bubbles (Figure 1). A sharp blade was used to remove the excess cement before setting from the top of the brass split mould. A layer of

Oxyguard II (oxygen - blocking gel) was applied in the case of Panavia F.

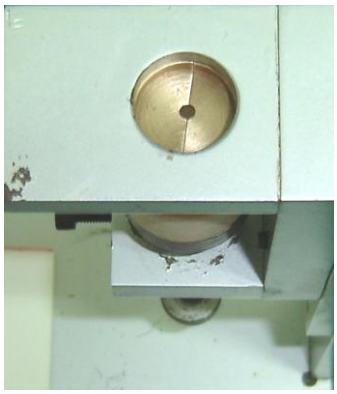

Figure 1: The hole in the brass mould adapted to the bending jig

Specimens were allowed to set under a constant load of 1 kg for 15 minutes using a polyvinylsiloxane (Express putty, 3M ESPE, St. Paul, MN, USA) putty mould that was placed over the brass split mould and held in place by the weight (Figure 2). The 1 kg load was removed, and the samples were allowed to sit at room temperature for an additional 30 minutes with the polyvinylsiloxane mould still in place.

Figure 2: Load application during bonding

The samples were carefully removed from the apparatus, and the brass split mould was separated using a sharp blade, and the excess cement was removed with a scalpel blade to standardise the bonding area. Then, the specimens were stored in distilled water at 37°C for 24 h before testing.

Testing procedure

The bonded specimens were mounted in the shear test jig recommended by ISO [15] and tested using a universal testing machine (Instron® Corp., England) at a crosshead speed of 1 mm/min (Figure 3).

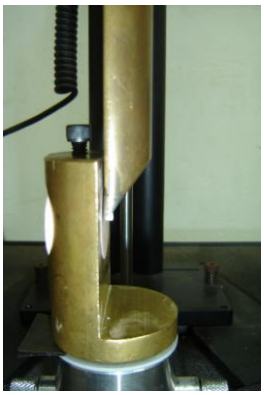

Figure 3: Specimen during shear bond strength testing

The maximum load at failure was recorded in Newton, and the SBS of each specimen was calculated and expressed in MPa by dividing the force (N) at which the bond failure occurred by the bonding area (mm^2).

Assessment of mode of failure

The bonded surfaces were observed under a microscope (Zoom Stereo EMZ - 1, MEIJI Techno Co., Ltd., Saitama, Japan) at 30X magnification to evaluate adhesive and cohesive failure modes. According to Piwowarczyk et al., (2004), failures were categorised as follows [19]:

1. Adhesive failure at the ceramic-cement interface.

2. Cohesive failure within the cement or ceramic.

3. Mixed failure: a combination of adhesive and cohesive failures.

Statistical analysis

Descriptive statistics of shear bond strength were performed. To compare shear bond strength between the four groups tested, One Way ANOVA and the nonparametric Kruskal - Wallis tests were conducted. A post hoc test using Mann - Whitney Post hoc test was performed to test which pair of groups differ from each other significantly.

Regarding the association between shear bond strength and modes of failure, descriptive statistics for modes of failure and shear bond strengths were recorded, and the result was descriptively analysed. The Statistical Package for the Social Sciences, version 19 (SPSS, SPSS Inc., Chicago, IL) software was used to perform the statistical analysis. Statistical significance was set at $\alpha = 0.05$.

Results

Descriptive analysis was performed, and the mean and median shear bond strength for all groups is presented in Table 1.

Table 1: The mean and median shear bond strength (MPa) for the four luting types of cement used

Cement	n	Mean (SD)	Median (IQR)	95% Confidence Interval	
				Lower Bound	Upper Bound
Elite	10	0.92 (0.42)	0.95 (0.59)	0.62	1.22
Fuji I	10	2.04 (0.78)	2.11 (1.21)	1.48	2.60
Fuji Plus	10	4.37 (1.18)	4.22 (1.06)	3.52	5.22
Panavia F	10	16.42 (3.38)	15.92 (4.20)	14.01	18.84

Since the distribution of shear bond strength was not normally distributed as indicated by histogram and Shapiro - Wilk test, nonparametric Kruskal - Wallis Test was then done to compare the shear bond strength between Elite, Fuji I, Fuji Plus and Panavia F. Results were shown in Table 2. There was a significant difference in shear bond strength between the four groups ($p < 0.001$).

Table 2: Comparison of shear bond strength (MPa) between Elite, Fuji I, Fuji Plus and Panavia F by Kruskal Wallis Test

Cement	n	Mean (SD)	Median (IQR)	Chi-Square (*df*)	*P* value
Elite	10	0.92 (0.42)	0.95 (0.59)		
Fuji I	10	2.04 (0.78)	2.11 (1.21)	34.837	<0.001
Fuji Plus	10	4.37 (1.18)	4.22 (1.06)	(3)	
Panavia F	10	16.42 (3.38)	15.92 (4.20)		

[A] Kruskal - Wallis Test was used. Significant level was set at 0.05.

Further analysis using Mann - Whitney Post hoc test with Bonferroni correction as multiple pairwise comparisons revealed that there were significant differences between shear bond strength of Elite and Fuji I ($p = 0.018$), Elite and Fuji Plus ($p < 0.001$), Elite and Panavia F ($p < 0.001$), Fuji I and Fuji Plus ($p < 0.001$), Fuji I and Panavia F ($p < 0.001$) and also between Fuji Plus and Panavia F ($p < 0.001$).

Testing mode of failure

A cross-tabulation was performed between the four treatment groups (Elite, Fuji I, Fuji Plus and Panavia F) and modes of failure. It was noticed that with Elite, Fuji I and Fuji Plus, the modes of failure were 100 % adhesive mode. While for Panavia F, the modes of failure were 30 % mixed and 70 % adhesive mode.

Descriptive summary for modes of failure and shear bond strengths was performed. The identified modes of failure were: adhesive and mixed. The shear bond strength for the adhesive mode of failure was in ascending order; Elite (0.92 MPa), Fuiji I (4.04 MPa), Fuji Plus (4.37 MPa) and Panavia F (14.79 MP). In general, the shear bond strength for the mixed mode of failure (20.25 MPa) was higher compared to that of the adhesive mode (0.92 to 14.79 MPa).

Discussion

This study was carried out to evaluate the shear bond strength of different luting cement (zinc phosphate cement Elite, glass ionomer cement Fuji I, resin-modified glass ionomer cement Fuji Plus and resin luting cement Panavia F) to Turkom-Cera all - ceramic discs.

The results of the current study indicated that the bond strength of resin luting cement Panavia F (16.42 ± 3.4 MPa) to sandblasted Turkom-Cera discs was higher to that obtained by zinc phosphate cement Elite (0.92 ± 0.4 MPa), glass ionomer cement Fuji I (2.04 ± 0.8 MPa) and resin-modified glass ionomer cement Fuji Plus (4.37 ± 1.2 MPa). Statistical analysis showed the statistically significant difference between the four luting types of cement tested. The mean shear bond strength of Panavia F was significantly higher than Elite, Fuji I and Fuji Plus ($p < 0.05$).

In interpreting the results of this study, one has to take into account the internal strength of the cement used. Ultimately, cement with a bond strength that competes with the strength of the cement or one of the substrates to be bonded to can be used. The bond strength of zinc phosphate and glass ionomer cement is much lower than that of resin-modified glass ionomer cement, which have a lower strength compared to resin composite cement [20]. This fact is reflected in the highest shear bond strength value of the resin cement tested in this study. In general, the ranking of the bond strength results increased up from zinc phosphate cement to glass ionomer cement to resin-modified glass ionomer cement to resin luting cement. This trend may be related to the intrinsic strength of the cement. The higher the resin contents, the higher the strength [21] [22].

The results of this study are in agreement with the results of other in vitro studies [19] [23]. Piwowarczyk et al., (2004) found that the shear bond strengths between sandblasted high - strength aluminium oxide ceramic and resin cement were significantly higher than those of zinc phosphate, glass ionomer and resin-modified glass ionomer cement [19]. Another in vitro study found that the shear bond strength of aluminium oxide-reinforced glass ceramic material increases significantly from conventional glass ionomer cement, resin-modified glass ionomer cements to resin cement [23].

In vitro studies on bonding strengths of cement to dental ceramics differ within a wide range and assessment of their clinical significance is difficult. Since the all-ceramic restoration is cemented to dentine, is not only the cement - ceramic interface important, but also the dentine - cement interface can be an important factor that determines the longevity of the restoration.

The shear bond strength of human dentine was found to be 13.4 MPa [24]. It has also been

suggested that 10 - 13 MPa is the minimum strength needed for clinical bonding [23] [25]. On the other hand, the in vitro bond strengths to acid - etched human dentine of various commercial resin composite bonding cement, which have been in clinical use for a relatively long time, are reported to range from 1.1 MPa to 14.8 MPa [26]. The shear bond strength of dentine to Panavia F and Fuji Plus were 7.7 MPa and 7.0 MPa, respectively [24] [27]. Due to variation in the experimental set - up or preparatory procedures, the shear bond strengths reported in the literature are difficult for comparison. Nevertheless, the shear bond values reported are much lower than the shear bond strength values found for the ceramic - cement interface. A microtensile bond strength test of dentine and a Cerec 2 inlay cemented with Panavia F showed a similar result; debonding occurred more often at the cement-dentine interface than at the cement - inlay interface [28]. This finding was also supported by another study which found that the resin composite had the higher bond strength to the ceramic material than to the prepared dentine [29].

In short, based on the previous considerations the use of the resin cement Panavia F will give the most reliable bond to the ceramic material, and fracture will most probably occur at the cement - dentine interface.

For conventional zinc phosphate cement, one study reported tensile bond strength to dentine of 0.6 MPa, whereas another study reported 0.9 MPa [30] [31]. Although these values seemed to be very low, and are considerably inferior to those suggested as the minimum acceptable strength for clinical bonding, zinc phosphate cements have been successfully used clinically for a very long time to lute cast dental restorations and currently recommended for luting high - strength ceramics (eggs: Procera AllCeram and Turkom - Cera) [11] [12] [13]. To assess the clinical performance of bonding systems, in vitro studies should, therefore, be supplemented with clinical studies with long-term follow-up.

The current study also addressed the issue of failure modes. About the luting cement used with sandblasted Turkom-Cera ceramic, failure modes for zinc phosphate, glass ionomer and resin-modified glass ionomer cement were completely adhesive between the cement–bonding substrate interface for all specimens. However, the Panavia F has shown a complex adhesive and cohesive failures in 30 % of specimens which was in agreement with another study conducted by Ayyildiz et al. in 2015 [33]. This complex mode of failure may explain the higher bond strength of Panavia F to Turkom-Cera specimens obtained in this study.

In conclusion, within the limitations of this in vitro study, it was found that the mean shear bond strength between sandblasted Turkom-Cera ceramic and Panavia F was significantly higher than those of zinc phosphate, glass ionomer and resin-modified glass ionomer cement. This study has given rise to the tentative conclusion that higher bond strength values increase complex (adhesive and cohesive) failure modes.

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Prevalence of Plaque-Induced Gingivitis in a Sample of the Adult Egyptian Population

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Abstract

AIM: The aim of this cross-sectional study is recording the prevalence and evaluation of the severity of plaque-induced gingival inflammation among a sample of the adult Egyptian population.

PATIENTS AND METHODS: Four hundred and twenty-five subjects in this contemplate were seen from patients visiting the diagnostic clinic at the Faculty of Dentistry, Cairo University. The gingival and plaque indices for each patient diagnosed as having plaque-induced gingivitis were recorded. The pocket depth was also measured.

RESULTS: The incidence of gingivitis was 100% amid adult subjects with an age range between 18-45 years. The average plaque index (PI) was 1.05 ± 0.43, which reflects relatively superior plaque control of the participants. The mean gingival index (GI) was 1.66 ± 0.40, which reflects the presence of moderate gingival inflammation. PD mean values confirmed limitation of inflammation to the gingiva. The sex was correlated to the condition of the inflamed gingiva ($p = 0.014$) and the quantity of biofilm build-up ($p = 0.003$). Females were less affected than males ($p = 0.005$).

CONCLUSION: The outcomes of this contemplate demonstrated that biofilm build-up is stoutly accompanied with elevated incidence of modest to rigorous gingivitis amid adult Egyptian individuals.

Introduction

Gingivitis is a reversible type of periodontal disease in which inflammation is limited to the gingiva without further destruction of the tooth-supporting components [1]. It is regarded as the second main and commonly occurring oral malady following dental caries, disturbing more than 75% of the populace global wise [2] [3] [4]. The incidence of gingival inflammation varies in the conducted studies among the different countries as a consequence of diversity in the studied populations, the age of the included subjects, and the methods of recognising and diagnosing this condition. Epidemiological studies discovered that plaque-induced gingivitis starts early in children, and becomes more common and aggressive with age and widely spreads among all ages [5] [6] [7] [8] [9]. It is caused by the increased accumulation of plaque biofilm near the gingival margins. The clinical features characteristic of this gingival inflammation are the erythematous and spongiotic texture of the gingiva; contour alterations; provoked bleeding; and occurrence of calculus, or plaque with no loss of clinical attachment, or radiographic substantiation of crestal bone resorption [10] [11]. Dental professionals advocated efficient oral hygiene measures to maintain optimal oral health aiming at controlling dental plaque and managing the inflammatory products liberated during the interactions between pathogenic microbiota and host response [12] [13] [4].

Clinically, the sternness and signs of the inflamed gingiva can be assessed by gingival index (GI) of Loe and Silness [15] [16]. In regards to this index, inflamed gingiva can be categorised as mild, moderate, or severe. The occurrence of these symbols of inflammation is regarded as the early phase of the more severe and irreparable form of periodontal destruction as in periodontitis cases. A subject's vulnerability to extend this form of the

disease also is greatly inconsistent and is dependent on the host retort towards perio-pathogens [17] [18] [19], which might be controlled by both acquired and genetic factors that can alter the vulnerability to infectivity [12] [20]. Avoidance of dental biofilm is amassing and untimely treatment of gingival inflammation diminishes the dangers aligned with the advancement of other serious and ruinous appearance of periodontitis [11] [21]. It is reported that gingivitis occurs past 10 - 21 days of biofilm amassing, [22] requiring a regular endeavour to counteract plaque accumulation. A few mulls over found a noteworthy relationship between diminishing the frequency of gingivitis and normal biofilm control procedures [23] [24] [25]. The aim of this study is record the incidence and to evaluate the rigorousness of plaque-induced gingivitis among a sample of the adult Egyptian populace.

Patients and Methods

The study protocol was approved by the Ethical Committee at the National Research Centre (NRC). Included subjects after explaining all the study procedures to them were asked to sign an informed consent stating their approval. Four hundred and twenty - five eligible participants in this contemplate were recruited from the routine dental patients who attended in the oral diagnosis clinic at the Faculty of Dentistry, Cairo University, Egypt. The medical history of each subject was recorded at the time of examination in a special recording form according to the Cornell Medical Index [26]. Exclusion criteria included subjects who were wearing fixed or removable prosthesis, or with orthodontic appliances. Also, subjects under current periodontal treatment, tobacco smokers, female subjects who were pregnant or using oral contraceptives were not included. Subjects with any other systemic conditions that are known to predispose, or exaggerate gingival inflammation, or any subject who was on antibiotics, antifungals, or antiseptic mouthwash for therapeutic reasons over the past 3 months, were not allowed to participate. A minimum of 20 permanent teeth had to be present for including the patient in the study.

The periodontal examination was performed by 2 dentists for all subjects in a dental chair, using a mouth mirror, and a calibrated Williams' periodontal probe [27]. Periodontal charting was made for all participants, and the data was recorded in a special diagnostic format. Periodontal health was defined as the complete absence of gingivitis at any site, and gingivitis was defined as inflammation of the gingiva in at least one site with the absence of clinical attachment loss [11]. Gingival health status was recorded for all study subjects using the gingival index (GI) of Loe and Silness [16]. Dental plaque status was also determined using plaque index (PI) of Silness and Loe [13]. Periodontal pocket depth was also assessed to exclude the presence of any evidence of crestal bone resorption using graduated Williams' probe and measured in mm. In accordance with the GI score, the subject's gingival health was assigned as follows: no inflammation (< 0.1); mild inflammation (0.1 - 1); moderate inflammation (1.1 - 1.9); and severe inflammation (2 - 3) [16]. For the PI score, the subject's plaque status was assigned as follows: excellent (< 0.1); good (0.1 - 0.9); fair (1 - 1.9); and poor (2 - 3) [13]. Oral hygiene care was conducted by the teaching of appropriate tooth brushing techniques and methods for plaque control.

Numerical data were presented as mean ± standard deviation (SD) values. Data were explored for normality using Kolmogorov - Smirnov test of normality. When variables were found to be normally distributed, independent student t-test was used to compare means of variables (clinical parameters) between the two groups (males and females). When variables were found to be non - normally distributed, Mann - Whitney test was used for comparing means of variables between the two groups. Data was collected and saved on a personal computer and analysed using the Statistical Package for Social Sciences (SPSS) software version 22 (IBM Corp, Armonk, NY, USA).

Results

The present study included 425 adult dentate subjects, 241 females (56.71%), and 184 males (43.29%), age range between 18 and 45 years with a mean age of 29.72 ± 6.41 years. The mean age for male subjects was 29.86 ± 6.85 years, which is not statistically significant than females age (29.56 ± 5.96) (p = 0.000). Participants were alienated into 3 groups as regards to their era variety as presented in Table 1.

Table 1: Demographic criteria of the subjects included in this study

Group	Age Range	Gender n (% of total)		Total no. of included subjects n (%)
		Males	Females	
1	18-25	32 (7.53)	130 (30.59)	162 (38.12)
2	26-35	62 (14.59)	67 (15.76)	129 (30.35)
3	36-45	90 (21.18)	44 (10.35)	134 (31.53)
Total		184 (43.30)	241 (56.70)	425 (100)

The average PI for the entire patients was 1.05 ± 0.43, which reflects a modest plaque status of the subjects. Male participants had more plaque buildup in comparison to females (p = 0.003) as presented in table 2 and figure 1. The average PI for males was 1.08 ± 0.44 and 1.01 ± 0.42 for females. Additionally, gingival healthiness and quantity of biofilm amassing were not correlated to the era of the examined participants (p = 0.53). The sex was

interrelated to the inflammation present (p = 0.014) and the quantity of biofilm buildup (p = 0.003). Females were less affected than males (p = 0.005).

Table 2: The plaque grade of the subjects included in this study

Plaque Status	Gender n (% of total)		Total	p-value
	Male	Female		
Excellent	4 (2.17)	18 (7.47)	22 (5.18)	0.063
Good	79 (42.92)	156 (64.73)	235 (55.29)	0.074
Fair	93 (50.54)	60 (24.89)	153 (36)	0.003*
Poor	8 (4.37)	7 (2.91)	15 (3.53)	0.122
Total	184 (43.30)	241 (56.70)	425 (100)	

*significant.

The outcomes of this contemplate revealed that 100% of all subjects presented with a variety of inflammation signs (GI scores were more than 0.1). The average GI score for participants was 1.66 ± 0.40, which shows a modest gingivitis. Females had fewer indications of gingival inflammation in contrast to males (*p* = 0.001) as revealed in Table 3 and Figure 2.

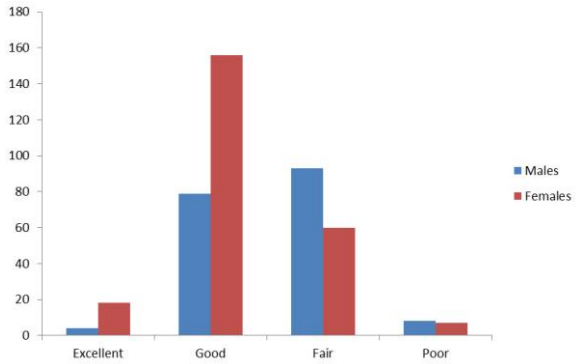

Figure 1: Histogram showing plaque scores among males and females

The mean GI for males was 1.72 ± 0.45, and 1.3 ± 0.35 for females. 110 patients (25.88%) had a GI score equivalent to 2, which demonstrates stern gingivitis and slight flow of blood on probing. Bleeding gingiva on probing was considerably lower in females 42.2% as compared with males 54.4% (*p* = 0.016).

Table 3: The gingival health status of subjects in this study

Gingival Health Status	Gender n (% of total)		Total	p-value
	Male	Female		
No inflammation	0 (0.0)	0 (0.0)	0 (0.0)	-------
Mild GI	4 (2.18)	23 (9.54)	27 (6.36)	0.003*
Moderate GI	102 (55.43)	186 (77.18)	288 (67.76)	0.014*
Severe GI	78 (42.39)	32 (13.28)	110 (25.88)	0.588
Total	184 (43.30)	241 (56.70)	425 (100)	-------

*significant.

Discussion

Assessing the prevalence of gingival inflammation caused by plaque biofilm accumulation in adulthood worldwide is complicated as a consequence of the variety of study populations, hereditary background, and contributing ecological factors. Additionally, the existence of various clinical methodologies for diagnosing and defining gingival inflammation and lack of evident objective cut-off points between health and disease add to the complexity.

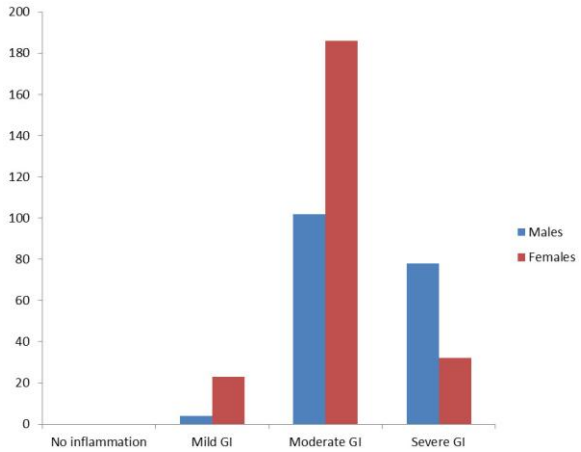

Figure 2: Gingival health status among males and females

Numerous previously conducted epidemiological contemplates revealed that the incidence of gingivitis in adults is changeable around 50-100% for dentulous subjects [5]. In the present contemplate; the incidence of gingivitis was 100% amid the examined participants with an age range between 18 and 45 years. Unlike various studies, there were no preliminary or washout periods or any oral hygiene education before the oral assessment. Subjects included did not change their diet or regular practice to diminish the effects of these parameters on dental plaque. Subjects did utilise dental treatment services only in case of pain or other emergencies [26] [27] [28] [29].

A study on Chinese subjects ageing between 18 and 90 years performed by Zhang et al. [27] revealed the presence of gingival inflammations in 97.9% of subjects examined. Also, Li et al. [29] documented that gingivitis was detected in 95.7% of American adult subjects with age ranging 18 - 90 years. A study conducted among the Saudi adult population by Idrees et al. 2014 [29] revealed the occurrence of gingival inflammations in 100%. This in line with the present results obtained in this contemplate which confirmed the presence of gingival inflammations in 100% of participants.

In two earlier investigations, the decisive factors for defining the presence of gingivitis was GI = 0.5, or above. Gingivitis should be detected at three sites or more to be regarded as inflammation. On the contrary, our criteria for pointing out gingivitis is its presence in at least a single location, or GI > 0.1 [29], and this revealed the elevated incidence of this condition in the present contemplate as comparable to other research results with this narrow age range (18 - 45 years) [27] [28].

In the present contemplate, the predominance of participants with gingival bleeding was 25.88%, and it was superior in men as compared to women. An elevated incidence of gingival bleeding in men was also recorded 2009 in Australia [30] among male participants who confirmed that the existence of accumulated plaque deposits is intimately related to the occurrence of gingivitis [13] [30] [31]. This is by the present study. The obtained results in this study are in line with earlier studies that clarified the significant correlation of sex with gingival illness and biofilm buildup [5] [27] [29]. This might be because men are less anticipated to visit the dental practitioner regularly with their poor state of mind towards wellbeing in comparison to females [32]. This contemplates demonstrated that era was not correlated with the presence of gingivitis and the measure of biofilm amassing. This might be due to the restricted age scope of included subjects in the vicinity of 18 and 45 years as in contrast to other conducted studies [5] [28] [29]. Also, firm prohibition criterions have been assumed to play a critical role to achieve these outcomes. As indicated by the World Health Organization, the era aggregate between 35 - 44 years was regarded as the principle set since the majority populaces at this age range showed signs of oral illness and diverse forms of periodontal diseases [33]. Furthermore, the occurrence of periodontitis rises with the era. Adults more than 50 years have the greatest jeopardy for being involved [33] [34]. Zhang et al. [28] confirmed that the age set older than 59 years had considerably superior GI in comparison to youth. Our outcomes are constant with a former contemplate that showed no interrelationships between era and gingival inflammation [29] [30]. The results are similar to a report published by the Saudi National Office of Statistics and a study conducted among the Saudi adult population [29].

The mean results for gingivitis had resemblance also to those revealed in former studies of 0.99 from Saudi Arabia, 1.23 from Swiss people, 1.2 from the Gambia, 1.05 from the USA, and 1.1 from China representing populations from different regions [35].

In a study conducted on 1650 adults from three South American cities, the results revealed 95.6% with a GI ≥ 0.5. This data corroborates the information presented for adults from Jordan and United States of America which showed 75.8% and 93.9% respectively [36].

In conclusion, this study despite its limitations demonstrated that plaque amassing is firmly connected with an elevated predominance of modest to severe gingivitis among the sample of the Egyptian subjects seen. Additional investigations are mandatory to perceive the causes that may add to this elevated incidence of plaque-induced gingivitis. Public preventive outlines ought to be evaluated and re-actualised on a broad and efficient level.

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Dental Science

Evaluation of Maximum Bite Force in Patients with Complete Dentures

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Abstract

OBJECTIVE: This study aimed to evaluate maximum bite forces (mBF) in dominant (DS) and non-dominant sides (NDS) at certain time periods after the insertion of new complete dentures based on prior experience and gender.

MATERIALS AND METHODS: A total of 88 patients, complete denture wearers (CDWs), were examined. The maximum bite force at the intercuspal position between the first molars in 3 seconds was registered and recorded with piezoelectric gnathodynamometer. The procedure was repeated 3 times in identical conditions, with relaxation intervals of 1 minute between repeats and the limiting factor was the subjective feeling of pain. Testing of parametric data was performed with One Way Repeated Measurement of ANOVA test.

RESULTS: The average mBF values increased during the observational period, both on the DS and NDS, with significant difference in DS, which was greater. The analysis of one-factor variance showed that there were differences of average mBF values in DS and NDS during six consecutive measurements (mBF–DS = 11.3, p = 0.0001, and mBF-NDS = 2.26, p = 0.047). Significant changes in the masticatory force (mBF) on the DS and NDS is explained by different measurement times and with the prior experience with complete dentures, BF–DS = 11.76, p = 0.0000; mBF–NDS = 2.42, p = 0.0351; mBFe–DS = 40.48; P = 0.0000 mBFe–NDS = 39.93, p = 0.0000.

CONCLUSION: mBF represents a significant discriminating variable of the level of functional adaptation of new complete denture wearers (nCDWs) about the initial measurements.

Introduction

Being edentulous is considered a handicap, both concerning the oral function and psychological impact. The restoration of masticatory function and aesthetics is an important aim in dentistry mainly when patients present with extensive tooth loss. The loss of teeth in elderly patients not only impairs the stomatognathic system but also their psychological status and quality of life [1] [2].

Complete dentures should, biologically, establish the relationship with the living tissues. During rehabilitation with prosthetic treatment, forces acting in the oral cavity should be considered, as well as, the way these forces are distributed through the dentures on the denture bearing areas [3]. Distribution of masticatory forces under physiological conditions is as follows: occlusal - articular complex → periodontium → bone foundation. However, the biological organisation of the orofacial system responsible for the distribution of bite forces is complex and differs from the physiological mode of pressure conveyance.

Various methods have been used to numerically assess the masticatory forces while chewing various foods [4]. It is thought that Black was the first researcher who used measurements and estimates of masticatory forces as well as having researched *in vitro* feeding with an instrument, which he nominated a phagodynamometer. Obtained values ranged between 90N and 360N [5]. Howell and Brudevold presented the method for direct measurement of masticatory forces in the oral cavity [6].

The influence of biting forces (BF) on the masticatory system is profound. Incomplete denture wearers (CDWs) consuming tough foods, bite forces

are reduced by 15% to 20% compared to healthy dentate patients, that is 40% [7]. The masticatory load in natural teeth is 200N while the maximum forces during mastication of CDWs range between 60N and 80N [8]. Tooth loss and its consequent prosthetic replacement not only decrease the BF between 20% to 50% compared to the natural dentition but is also associated with other problems such as eventual bone loss [9]. According to De Boever, only 4% of functional forces are utilised, while the maximum bite force (mBF) values during mastication do not exceed 22% of their capacity [10]. Muscle force and the number of functional teeth are determinant factors in mastication. Measuring mBF is an attempt to quantify the force that mandibular elevator muscles can make [11]. The magnitude of bite force has shown to be correlated to the patients' satisfaction with complete dentures, type of food, and the amount of bone resorption under prostheses [12].

This study aimed to evaluate the maximum bite force (mBF) in the dominant side (DS) and non-dominant (NDS) at specific time periods after fitting of new complete dentures based on patient's prior experience and gender.

Material and Methods

A total of 88 patients with complete dentures were included in this study. The research was accepted and approved by the Ethics Committee, School of Dental Medicine, University of Prishtina, Kosovo, and written consent was obtained from each subject.

The research was divided into two experimental groups and compared to experienced complete denture wearers (eCDW). Group 1 consisted of inexperienced (first time) complete denture wearing patients (iCDW) fitted with maxillary and mandibular complete dentures; Group 2 consisted of experienced patients with complete dentures (eCDW). The patients were pooled at the Department of Prosthodontics, Dental School, Faculty of Medicine, the University of Prishtina in Kosovo. After fitting the new complete dentures, all patients were tested for mBF at the intercuspal position. Patients were followed for 6 months. During this period, stabilisation of complete dentures was expected. During the observation period, each subject was measured six times within six months. The first measurement was performed one week after the fitting of the complete dentures, and successive recalls at 2 to 5 weeks, 3 to 10 weeks, 4 to 15 weeks, 5 to 10 weeks and 6 to 25 weeks.

During measurements, patients were invited to sit on a chair in a quiet room so that the Frankfurter plane was approximately horizontal. This test included recordings of the mBF at the intercuspal position between the first molars for 3 seconds with a piezoelectric gnathodynamometer. The procedure was repeated 3 times in identical conditions, with relaxation intervals of 1 minute between repeats and the limiting factor was the subjective feeling of pain.

During each measurement of one side of the jaw, to stabilise the complete dentures during the test, the rubber cylinder was applied on the contralateral side at the first molar region, with 75% hardness according to Shore with the same width as the Gnathodynamometer probe (6 mm). The piezoelectric gnathodynamometer was directly connected to a DynoFigure printer. In this way, apart from the numerical values of the bite forces, Figural data were recorded as well. In the Figural data, the mBF was represented by a basic line of deflection. For the evaluation of the results, the highest expressed value of mBF was recorded. The jaw side, showing greater mBF during measurement was referred as the dominant side (DS), while the opposite as the non-dominant side (NDS).

Statistical analysis was performed using standard software package BMSP (BioMedical Statistical Package), dedicated to research in the biomedical sciences, which included all methods of statistical procedures, (Dixon, 62.). Testing of parametric data was done with One Way Repeated Measurement of ANOVA test.

Results

The basic parameters of bite forces at defined time intervals (N) were presented in tabulated and Figural forms. It can be concluded that the average values increased during the observational period, both on the DS and NDS. Higher values were recorded for the DS with a significant statistical difference. The analysis of one - factor variance showed that there were differences in average values between DS and NDS for the six measurements (mBF - DS = 11.3, p = 0.0001, and mBF - NDS = 2.26, p = 0.047). This indicator showed that on both sides the initial value of mBF changed over time (Table 1, Figure 1).

Table 1: Basic parameters of Maximum Bite Force (mBF) in Set Time Intervals on Dominant (DS) and Non - Dominant Sides (NDS) of the sample (N)

	Maximum Bite Force (mBF) Dominant Side (DS)						Maximum Bite Force (mBF) Non-Dominant Side (NDS)					
Measur.	1	2	3	4	5	6	1	2	3	4	5	6
N	88	88	88	87	88	88	88	88	88	87	88	88
X	138	178	200	208	211	202	102	111	121	119	127	126
Xmin	24	48	64	40	52	60	24	30	34	30	40	44
Xmax	348	392	412	526	416	448	312	290	300	356	320	360
DS	90.1	74.3	74.8	83.9	75.7	73.2	3.5	54.2	55.0	55.7	54.2	50.8
GS	9.6	7.9	8.0	9.0	8.1	7.8	6.8	5.8	5.9	6.0	5.8	5.4

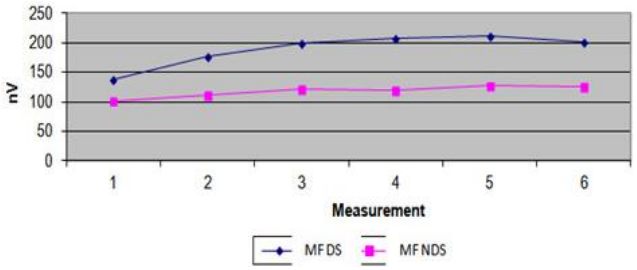

Figure 1: Masticatory Force in Set Time Interval (STI)

By analysing two variance factors (Gender and Time [of mesurement]), the influence of masticatory forces on DS and NDS were investigated. The resulting masticatory forces, for both sides, were influenced by the same factors, with significant difference (Table 2, Figure 2).

Table 2: Maximum Bite Force (mBF) in six Set Time Intervals (STI) in Females (F) and Males (M) on Dominant (DS) and Non - Dominant Sides (NDS)

Sex	Meas	Masticatory Force (mBF) Dominant Side (DS)						Masticatory Force (mBF) Non-Dominant Side (NDS)					
F	N	42	42	42	42	42	42	42	42	42	42	42	42
	X	61	133	156	153	162	170	53	84	85	88	95	101
	Min	24	48	64	40	52	60	24	30	34	30	40	44
	Max	100	202	270	282	290	288	100	160	150	140	160	150
	DS	16.9	40.7	44.7	57	54.2	51.9	17.7	28.9	25.2	27.4	26.7	25.4
	GS	2.6	6.3	6.9	8..8	2.7	4.4	3.9	4.2	4.1	3.9	3.2	3.0
M	N	46	46	46	46	46	46	46	46	46	46	46	46
	X	207	219	240	247	249	249	147	150	153	148	155	149
	Min	84	80	108	128	120	122	66	76	80	90	76	80
	Max	348	392	412	416	416	448	312	290	300	356	321	360
	DS	70.3	74.8	79.7	68.4	69.7	55.8	53.3	55.1	59.7	57.3	57.0	57.4
	GS	10.4	11.0	11.0	11.9	10.1	10.3	8.2	7.9	8.1	8.9	8.4	8.4

Gender: mBF - DS (gender) = 318.43, p=0.0000; mBF - NDS (gender) = 219.89, p = 0.0000. Time: mBF - DS (time) = 18.74, p = 0.0000; BF - NDS (time) = 3.83, p = 0.0020. Interaction: mBF - DS (inter) = 3.68, p = 0.0208, BF- NDS (inter) = 2.7, p = 0.201.

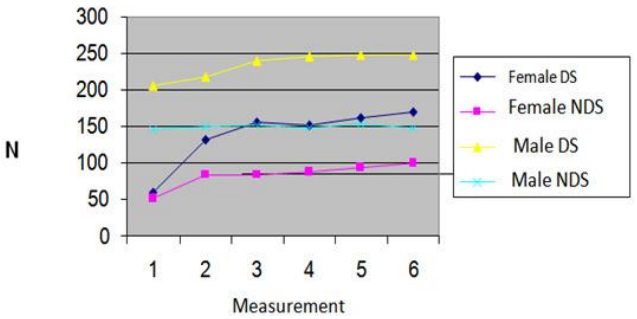

Figure 2: mBF at STI by Gender

Significant differences in the masticatory forces on DS and NDS is explained by different measurement times and with the prior experience wearing complete dentures. However, the interaction of these two factors had a significant impact on the variations in the masticatory force (Table 3, Figure 3).

Table 3: Maximum Bite Force (mBF) in six Set Time Intervals (STI) in Experienced Complete Denture Wearers (eCDW) and Inexperienced Complete Denture Wearers (iCDW) on Dominant (DS) and Non - Dominant Sides (NDS)

		mBF (DS)						mBF (NDS)					
	Msr	1	2	3	4	5	6	1	2	3	4	5	6
iCDW	N	45	45	45	44	45	45	45	45	45	44	45	45
	X	155	194	221	229	230	232	118	132	136	131	143	140
	Min	30	58	78	50	64	74	28	38	42	36	50	54
	Max	348	392	412	416	416	448	312	290	300	356	320	360
	DS	96.9	82.5	80.2	88.1	77.6	77.1	69.3	56.8	60.0	63.1	61.2	60.5
	ES	14.4	12.3	11.9	13.3	11.6	11.5	10.3	8.5	8.9	9.5	9.1	9.0
eCDW	N	43	43	43	43	43	43	43	43	43	43	43	43
	X	119	162	178	175	184	189	86	104	104	107	110	112
	Min	24	48	64	40	52	60	24	30	34	30	40	44
	Max	278	302	320	338	324	334	218	248	216	232	218	196
	DS	79.3	61.3	62.3	70.3	66.6	62.6	52.7	47.9	44.1	44.3	39.9	33.1
	ES	12.1	9.4	9.5	10.7	10.2	9.6	8.0	7.3	6.7	6.8	6.1	5.0

Time: mBF - DS (time) = 11.76, p = 0.0000; mBF - NDS (time) = 2.42, p = 0.0351; mBF - DS (experience) = 40.48; P = 0.0000; mBF - NDS (experience) = 39.93, p = 0.0000; Interaction: mBF - DS (inter) = 0.22, p = 0.9533; mBF - NDS (inter) = 0.09, p = 0.9941

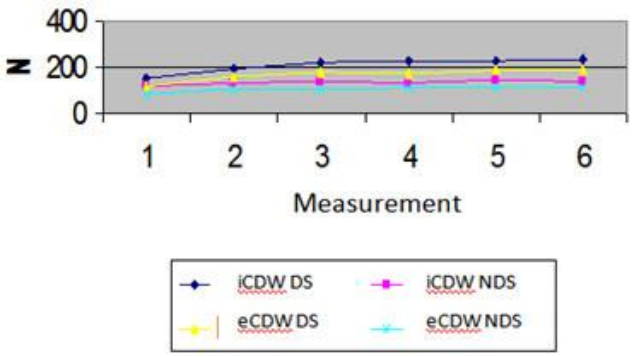

Figure 3: mBF at STI by Experienced and Inexperienced Complete Denture

The measurement time refers to the increase in average values of the masticatory forces in relation to the initial values and since the interaction was insignificant, this means that the same or approximate increase of masticatory forces occurs in eCDW and iCDW.

Experienced Complete Denture Wearers (eCDW) sooner reach the stationary state than Inexperienced Denture Wearers (iCDW) that reach it at their third measurement. The decrease of the values of the masticatory forces in CDW is explained by the fact that the patients lack their natural teeth. Patient age seems to be the cause of the reduction of masticatory forces.

Discussion

For over a century, conventional dentures were the sole treatment option for compromised dentitions. However, the rehabilitation of these patients using conventional dentures, regardless the quality, failed to completely solve either functional or psychological problem [13].

Most authors agree that the mBF increases significantly with newly fit complete dentures. However, the period towards reaching stationary state varies greatly. The results of this study indicate that after fitting of complete dentures the stationary state is reached after the 15th week, and it remains the same until the end of the observation period. Our results support previous findings which state that this period is between 12 and 24 months [14]. A stationary state is influenced by internal factors (fitness, the degree of reduction of the mucosal base, soft tissue condition, the presence of dysfunction) and external factors (related to prosthetic treatment). Niwatcharoenchaikul *et al*. concluded that complete dentures with bilateral balanced occlusion had no significant difference between masticatory performance and move [15].

Various authors (1944) concluded that people prefer unilateral mastication lean towards lateralisation of bite forces. Thus, in these patients, the masticatory force is higher on the preferred side versus the opposing side of the jaw [16] [17] [18] Some authors failed to observe the latter phenomenon [19], nevertheless it has been verified that people with full intact dental arches present with both Ds and NDS, as was also the case with our paper. This fact indicates that there is a preferred side in the functional sense even though the individual is unaware of it. Based on these findings it may be concluded that in the region of the first molar (centre of mastication), in CDW, the bite forces and the duration of the functional loads are greater on the DS versus the NDS. The speed of achievement of masticatory balance in DS and NDS varies. Bite forces in the DS reach the stationary state at the third measurement with no significant changes by the end of the measurements.

Gender does influence the variations in the dynamics of biting. Average values of masticatory forces are lower in females than males. At the time of measurement, there is a difference in the masticatory forces compared to initial values, followed by the stationary state. The influence of combined factors (interaction) is a more pronounced interval between initial and stationary ranges (DS = 109N, NDS = 48N) in females, while in males this change is less pronounced (DS = 42N, NDS = 38N). Probably, males respond faster to newly fit complete dentures regarding functional adaptation compared to females. This is consistent with the previous findings, which revealed a significant difference in gender. Higher mBF in males may be attributed to the larger size of their teeth and the greater muscular potential, therefore anatomical features may come in play. Larger teeth have larger periodontal ligament areas yielding greater biting forces [20] [21] [22]. In contrast, Wichelhaus *et al*. [23] have found no significant difference in mBF between males and females. Most studies have confirmed the differences of mBF values between males and females [20] [24] [25]. In the dynamics of maximum bite forces during observation period, a significant impact was experienced by CDWs. The results of this research have shown that eCDWs have higher initial values of maximum bite force (~ 40 N), and they consequently have better functional adaptation versus new CDWs. Over time, eCDWs have developed regulatory control mechanisms (memory paradigm of previous experience) which are used to compare e test new complete dentures. This minimizes the inhibitory impact of psychological factors and ensures imminent acceptance of complete dentures. Conversely, iCDWs are more cautious during neuromuscular adaptation period, although at the end of the observational period they have higher mBF. Dentists tend to believe that eCDWs, if positive, may readily adapt to new dentures; if negative, may poorly respond to adaptation. Furthermore, duration of denture use was associated with higher satisfaction rates [26].

Rehabilitation of edentulous patients with implant supported dentures is a very invasive and expensive long treatment option [27]. However, the biting forces and masticatory performance increased probably due to improved denture retention and stability [28]. Measurement of bite force has been a reliable method for assessment of the biomechanical properties of the masticatory system and prosthetic treatment. However, one should consider other effective factors when comparing bite force measurement in research [29]. The role of Prosthodontists is to have an understanding of the changes in the orofacial form, function and behavioural consequences and the possible social impact emerging from the complete loss of teeth [30].

Maximum bite force (mBF) represents a significant discriminating variable of the functional adaptation level to new complete dentures. The highest value of this variable is featured by the longer time intervals of function about the initial measurements and is the indicator of better adaptation to the new complete dentures. The region of the centre of occlusion on the DS has greater potential regarding transferring maximum physiological loads relative to the homologous part of the NDS. For the dynamics of this indicator, the progressive increase of values about the initial values with a tendency of restoring the stationary condition after the seventh week of delivery of the new complete dentures is remarkable.

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Dental Science - Case Report

Therapeutic Challenge in a Severely Atrophic Mandible

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Abstract

BACKGROUND: After tooth loss, however, severely atrophic residual alveolar ridges are fairly common, especially in patients who have been edentulous for a long period. Anterior area of the mandible is areas where clinicians have greater anatomical limitations. Reduced alveolar bone height very often represents a contraindication to implant therapy, unless a procedure such as a ridge augmentation is performed.

CASE REPORT: This study aims to present two separate cases in highly selected edentulous anterior mandibular sites, where one stage, mini implants were used to support total prostheses. Small diameter implants have been used for retention of complete removable mandibular overdentures. This is an excellent option for those who suffer from the inconvenience and embarrassment of loose lower dentures and are tired of having to use sticky pastes and creams to make their dentures stay in place.

CONCLUSION: Small diameter implants, when used multiples may offer adequate support for a removable prosthesis and overcome this problem.

Introduction

The management of the atrophic mandibular ridge has always been a challenge for the clinicians because of inadequate retention and support that the ridge offers to the complete denture prosthesis.When the complete denture patient is unable to tolerate the prosthesis in spite of all efforts from the clinician, the surgical approaches must be resorted to; these include the vestibuloplasties and the bone grafts [1].

The conventional removable total prosthesis has a frequent motion during the act of eating, chewing, swallowing and even talking. According to some statistic data, 50% of patient report those problems and 40% of them are located in the mandible, due to progressive bone resorption (Figure 1).

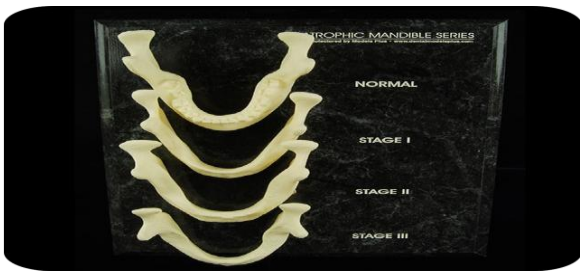

Figure 1: Resorption process in the mandible

The new method of treatment and its purposes include the following parameters: Mini Dental Implants (MDI) anchor the existing upper or lower dentures and provide stability. They are suitable to replace single or multiple missing teeth, and the patient can be prepared for fixed porcelain crowns after eliminating dentures entirely. The final goal is to eliminate the partial metal denture.

MDI is characterized by small diameter- for minimally invasive insertion (2 mm – D1 and D2/over 2.4 mm - D3 and D4); high purity, blasted and etched surface - for safe osseointegration; self - tapping thread - for quick and easy application, and two different connectors (ball top and cone top) - for large range of indications.

Mini Dental Implants vs Regular Dental Implants

MDI has many advantages over regular dental implants. They are much smaller than conventional implants (2 mm as against 4 mm - 5.75 mm for conventional implants), so it takes less drilling of the jaw bones. MDI surgery is minimally invasive. The surgery does not usually need cutting of gums and removal of stitches afterwards. Trauma to the jaw bone, bleeding, chances of injury, post-surgical discomfort are all minimised. Due to their smaller size, mini dental implants can also be used when the site for implantation is too narrow for a regular implant. Quite often, only local sedation of the implant site is needed in the case of MDIs.

The MDI procedure is quick and can be completed in one sitting as opposed to conventional implants which require several visits to the dentist [2] [3].

MDIs cost less than conventional dental implants, but offer advanced prosthesis stability and retention. The easy approach allows improved implant's hygiene. MDIs can improve facial structure restoration, prevent further bone resorption and provide immediate function.

Who is a Candidate for Mini Dental Implants?

Almost anyone with weak gums and in need of dental implants can go for mini dental implants. On the other hand, mini dental implants are not advised in the following situations: Uncontrolled diabetes, history of radiation treatment for cancer (this does not include X - rays for diagnostics), substance abuse, immune - suppression. Patients with the following conditions may suffer complications or failure with MDIs: heavy smoking/drinking habits, Sjorgren's syndrome, Alzheimer's disease, people who clench/grind their teeth, young persons in their growing years.

Preoperative Planning

General anamnesis, systemic disease evaluation, RTG imaging, CT - scan, 3D - implant planning are critical in preoperative planning procedure. Following these protocols, a measurement of the crest between the mental foramen of edentulous mandible should be performed, and attention should be paid to the following parameters: - processes alveolaris volume, thickness and inclination; - bone density; and - implant marking (6mm space between implants).

MDIs can be successfully used in highly selected sites where there is adequate bone density and bone volume for immediate implant stability [5] [6]. Atrophic residual alveolar crest cannot be an option for standard two-stage implants with diameter from 3.75 – 4.2 mm. A series of mini implants (4 - 6) are placed along the gum line, and they serve as the base of the denture. At least 2 implants may be successfully used to support fixed partial and total dentures in edentulous sites of compromised bone width or length. The small size of mini implants often means that no incision is needed to place the implants. They can usually be inserted right through the gum into the bone. This eliminates the need for a recovery period, and the restoration can usually be placed right away or only a short time after.

One Stage Dental Implants

In the one-stage dental implants surgery, the second stage is altogether avoided, and during a single surgery, the implant is placed in the jaw bone is such a way that the top of the implant is higher than the surface of the bone, at the height of the soft tissue. When the soft tissue is stitched at the end of the surgery, the dental implant's head is exposed. There is, therefore, no need for a second surgery as the implant is already exposed and takes its place naturally [7].

Features of the One Stage Dental Implants are: osseointegration begins immediately; a short period of bone healing before placing the implant; there are no missing teeth in the mouth, and the tooth looks natural while the implant is healing.

Case reports

Case report 1

Fifty-nine years old female patient referred to our clinic with only one periodontally affected teeth remained in the mandible (Figure 2a). Three weeks after teeth extractions (Figure 2b), two cone top one - stage dental implants were inserted intraoperatively, with raising a mucoperiosteal flap (Figure 2c). One week later, implant supported total prosthesis was adapted after cementing Dodler bar attachment construction (Figure 2d and 2e). The retention and stabilisation were satisfying for the patient, resulting in optimal aesthetics and function (Figure 2f).

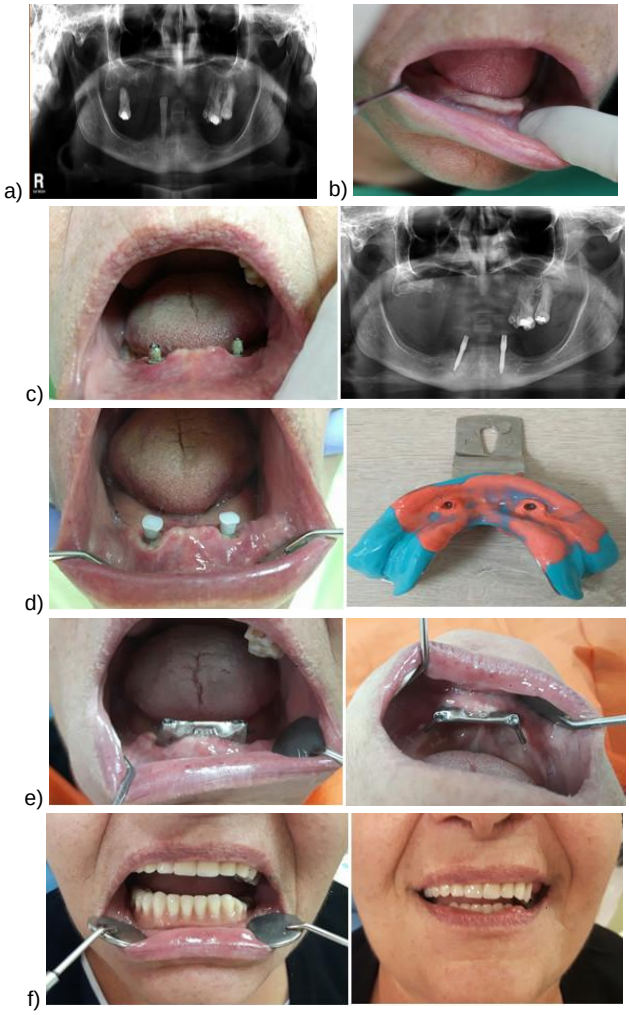

Figure 2: a) RTG view before extraction; b) Clinical situation after healing; c) Inserted two cone top dental implants, clinical and RTG view; d) Positioning the transfers for impression; e) Fixing total prosthesis on Dodler bar construction; f) Final position on the total prosthesis

Case report 2

Sixty-two years old female patient was unsatisfied with an existed total prosthesis, due to uncontrolled motion and difficult function during the act of eating and even talking. The RTG status of both jaws is presented in Figure 3a. Two MDIs dental implants were placed in the frontal mandible (Figure 3b) and then connected with a bar attachment. A new prosthesis was adapted to a new cemented implant supported construction (Figure 3c). Improved stabilisation and prosthesis retention were achieved after the implant and prosthetic treatment (Figure 3d).

Discussion

A small diameter implant presents less of an obstacle for angiogenesis, and there are less percutaneous exposure and bone displacement as compared with standard sized implants [8]. Multiple splinted implants may be necessary to minimise metal fatigue from cyclic loading. Anterior restorations supported by mini implants may need occlusal relief to minimise the effects of cyclic loading [7] [9]. Because MDIs are one - piece fixtures and are immediately loaded, it is important to avoid lateral loads on the fixtures that may lead to failure of the implant to integrate and loss of the fixture. The teeth in the posterior region must be with an oval and narrow shape to minimise the axial and nonaxial forces [10] [11].

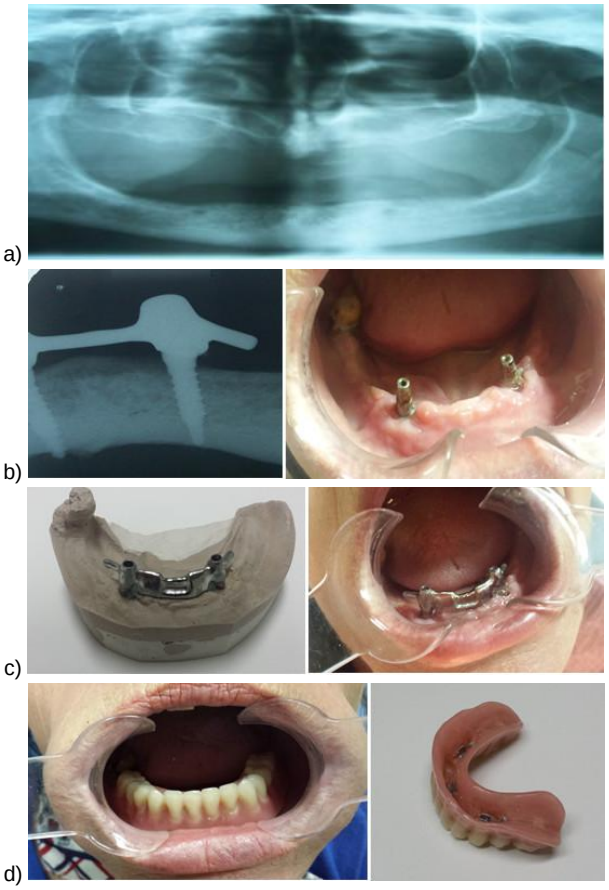

Figure 3: a) Radiological view of the residual alveolar crest in the mandible; b) Inserted two MDIs in the anterior mandible (RTG and clinical image); c) Adapting total prosthesis on implant-supported bar construction; d) Advanced retention and stabilisation of the prosthesis

The resultant stress distribution was evaluated by Flanagan in patients with total prosthesis supported by 2 implant bar-retained [12] [13]. Overlay denture was simulated with 0-, 1-, 2-, and 3-mm bar heights. A vertical force was applied to the left first molar and gradually increased from 0 to 50 N. The amount of stress transferred by 3-mm heights of the bar connection was greater than that of 1- and 2-mm bar connections [14].

In conclusion, this kind of method by using one stage dental implants provides satisfying retention and stabilisation of the removable overdentures, to achieve better comfort and quality during mastication

and other functions. The preferred technique for the practitioners is with transmucosal drilling and implants positioning. The major indications for MDIs usage are due to their affordable dimensions which offer some prosthetic options.

Because an increased number of implants are recommended when mini implants are planned as an anchorage device, a proper stress distribution on dental implants is necessary for the bar - retained implant overlay dentures. Dolder bar attachment with 1- and 2-mm heights could be associated with appropriate stress distribution for the implant-retained prosthesis.

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Dental Science – Review Article

Acid Etching as Surface Treatment Method for Luting of Glass-Ceramic Restorations, part 1: Acids, Application Protocol and Etching Effectiveness

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Keywords: Acid etching; Ceramic surface treatment; Hydrofluoric acid; Acidulated phosphate fluoride; Ammonium hydrogen bifluoride

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Abstract

AIM: The purpose of this review is to represent acids that can be used as surface etchant before adhesive luting of ceramic restorations, placement of orthodontic brackets or repair of chipped porcelain restorations. Chemical reactions, application protocol, and etching effect are presented as well.

STUDY SELECTION: Available scientific articles published in PubMed and Scopus literature databases, scientific reports and manufacturers' instructions and product information from internet websites, written in English, using following search terms: "acid etching, ceramic surface treatment, hydrofluoric acid, acidulated phosphate fluoride, ammonium hydrogen bifluoride", have been reviewed.

RESULTS: There are several acids with fluoride ion in their composition that can be used as ceramic surface etchants. The etching effect depends on the acid type and its concentration, etching time, as well as ceramic type. The most effective etching pattern is achieved when using hydrofluoric acid; the numerous micropores and channels of different sizes, honeycomb-like appearance, extruded crystals or scattered irregular ceramic particles, depending on the ceramic type, have been detected on the etched surfaces.

CONCLUSION: Acid etching of the bonding surface of glass - ceramic restorations is considered as the most effective treatment method that provides a reliable bond with composite cement. Selective removing of the glassy matrix of silicate ceramics results in a micromorphological three-dimensional porous surface that allows micromechanical interlocking of the luting composite.

Introduction

The increasing use of ceramic materials in the fabrication of indirect restorations as well as placement of orthodontic brackets on teeth restored with ceramic crowns imposed a need for improvement of cements that enable bonding [1] [2]. The most appropriate are luting composites [3] [4] which not only provide the strongest bond but can increase the fracture resistance of the restored tooth and indirect ceramic restoration as well [3] [4] [5] [6] [7].

However, to ensure a long-term bond between ceramic material and tooth structures, orthodontic brackets or composite material used for repair, treatment of ceramic bonding surface is required [8]. There are various methods for the stated purpose. According to the mechanism of action, they could be grouped into three categories: methods of mechanical, chemical or chemo-mechanical surface treatments. The mechanical alteration can be achieved by surface acid etching, airborne particle abrasion or grinding with diamond rotary instruments [8] [9]. The chemical treatment is performed using

universal or ceramic primers, i.e. silanization [10] [11], while the method used for chemo-mechanical alteration of the bonding surface is tribochemical silica - coating, i.e. silicatization [12] [14]. Numerous alternative treatments are proposed for treatment of restorations made up from zirconia such as: selective infiltration etching (SIE) [15] [16] followed by application of various silane-based zirconia primers [17] [18], gas - phase chloro -silane pretreatment [19], gas - plasma, argon - ion bombardment, alumina or zirconia sandblasting [20], [21], non - termal plasma treatment [22], nano -structure alumina coating [23] or aluminium nitride coating by reactive magnetron sputtering [24].

Which surface conditioning method will be selected depends on the chemical composition of the ceramic restoration [8] [25] [26]. Ceramics the matrix of which is based on silicon dioxide ("conventional" or glass - ceramics) belong to the group in which acid etching is the recommended surface treatment [26]. These include feldspar - based, leucite-reinforced, lithium disilicate [25] [26] and zirconia-reinforced lithium silicate ceramics [26] as well as fluorapatite ceramics. Airborne particle abrasion (sandblasting) can be used for surface treatment of all types of ceramics [9] [14] [20] [21] [26]. Universal or ceramic primers having reactive radicals in their molecule change the chemical composition of the ceramic surface, thus making it much more reactive for binding with composite cement [8] [10] [11] [26]. Tribochemical silica - coating is primarily used for the treatment of aluminium trioxide and zirconium dioxide ceramics [14] [16]; acid etching will not have any impact on their surface morphology, as these materials don't contain silicon in their composition [9].

Acid etching as a method for mechanical alteration of glass - ceramic surface, application protocol and the effect on surface micromorphology are presented in this review paper.

Etching Acids

The acid etching of silica-based dental ceramics was first introduced in 1983 by Simonsen and Calamia [27]. Although acids represent chemical agents, they are not included in the group of agents for a chemical but in those for mechanical alteration, because they cause a mechanical type of changes onto the ceramic surface.

The acids that are used as ceramic etchants are the hydrofluoric acid (HF), the acidulated phosphate fluoride (APF), and the ammonium hydrogen difluoride.

The hydrofluoric acid is the most frequently used acid, which when applied onto the ceramic surface reacts with the silica matrix creating silicon tetrafluoride and molecules of water that are released [8] [28]:

$$\underset{\text{Hydrofluoric acid}}{4\ HF\ (l)} + \underset{\text{silica matrix}}{SiO_2\ (s)} \rightarrow \underset{\text{silicon tetrafluoride}}{SiF_4\ (g)} + \underset{\text{water}}{2H_2O(l)}$$

The silicon tetrafluoride reacts with other molecules of hydrofluoric acid forming a soluble complex ion, hexafluourosilicate:

$$\underset{\text{HF acid}}{2\ HF\ (l)} + \underset{\text{silicontetrafluoride}}{SiF_4\ (g)} \rightarrow \underset{\text{hexafluourosilicate}}{[SiF_6]^{2-}\ (aq)} + \underset{\text{hydrogen ions}}{2H^+(aq)}$$

Further on, the hydrogen ions react with the hexafluorosilicate complex forming a fluorosilicic acid that can be rinsed off:

$$\underset{\text{hexafluorosilicate}}{[SiF_6]^{2-}\ (aq)} + \underset{\text{hydrogen ion}}{2\ H^+\ (aq)} \rightarrow \underset{\text{fluorosilicic acid}}{H_2SiF_6(l)}$$

By dissolving and removing the surface layer of the glassy matrix containing silica (SiO_2), silicates (SiO_4^{4-}) and leucite crystals ($K_2O{\bullet}Al_2O_3{\bullet}4SiO_2$), the surface becomes porous with a pore size of 3 - 4 μm.

The acidulated phosphate fluoride contains 1.23% fluoride ions originated from sodium fluoride and hydrofluoric acid, acidified with 0.1 M phosphoric acid [8].

The ammonium hydrogen difluoride, NH_4HF_2, in reaction with silica matrix creates silicon tetrafluoride and ammonium fluoride:

$$SiO_2 + 4\ NH_4HF_2 \rightarrow SiF_4 + 4\ NH_4F + 2\ H_2O$$

This acid may be used as a glass etchant or as an intermediate for the production of hydrofluoric acid [8].

There are different products that may be used for ceramic etching. It should be noted that, besides their efficiency, these products are forbidden in some countries because of their highly toxic potential.

Products for Acid Etching

IPS Ceramic Etching Gel, Ivoclar Vivadent [29], is an aqueous solution of 4% hydrofluoric acid in the form of a gel, unlike VITA CERAMICS ETCH, VITA Zahnfabrik [30], which is an alcoholic solution of 5% hydrofluoric acid and 10% sulfuric acid in the form of a gel. Porcelain Etch, Ultradent [31], is 9% hydrofluoric acid gel; mainly because of its high viscosity, according to the manufacturer's instructions, it may be used for intraoral repairs of fractured porcelain in porcelain – fused – to - metal or all-ceramic restorations, as well as for the porcelain surface treatment before placing an orthodontic brackets. PORCELAIN ETCHANT, Bisco [32] [33], can be supplied in two different concentrations, like 4% and 9.5% of hydrofluoric acid gel (for intra - or extra - oral application). Mirage offers two different Porcelain Etchants [34]: 9.6% gel of HF acid and 4%

Acidulated Phosphate Fluoride gel. APF - gel may be used intra -orally and is indicated for luting of orthodontic brackets to porcelain crowns.

Application Protocol

After the application, which is performed with a disposable micro brush, IPS Ceramic Etching Gel or VITA CERAMICS ETCH are left to react for 20 s when treating lithium disilicate and 30 s for zirconia-reinforced lithium silicate ceramic, 60 s for feldspar - based or leucite-reinforced and 120 seconds for treatment of fluorapatite ceramics. Then, HF acid should be thoroughly rinsed off from the treated surface with water spray into a polyethylene cup. The diluted solution should be neutralised with a neutralising powder composed of sodium - and calcium - carbonate (Na_2CO_3 and Ca_2CO_3; IPS Neutralizing Powder, Ivoclar Vivadent) in 5 minutes [35]. Eventually, the restoration is recommended to be placed in an ultrasonic bath. To remove the porcelain salts and debris formed by treatment with Porcelain Etch (90 s - etching time), Ultradent recommends a subsequent use of 35% phosphoric acid, Ultra-Etch, for 5 seconds; then, the treated restoration should be rinsed with water and dried [31].

Etching Effect

The effect of acid etching depends on the acid type and its concentration, the etching time and the ceramic type being treated. The most effective is hydrofluoric (HF) acid [8]; increasing the concentration and the etching time [36], increases the etching effect. Surface roughness and etching pattern depend on the ceramic type as well; acids do not affect polycrystalline ceramics that do not contain glassy matrix [9][14]. Contrary, the silica matrix and leucite crystals are selectively dissolved in glass-ceramics, generating three-dimensional porous structure [9][37]. The effect is multiplied: cleanses the bonding surface by removing the unwanted oxides, debris and grease [38], increases the roughness thus increasing the bonding area and wettability of the ceramic surface [39], and creates micro retention (micropores, grooves and channels) that can be easily infiltrated with uncured flowable composite cement [40][41], all together significantly increasing the resin - ceramic bond strength.

Acid type: The expressiveness of the surface micromorphology after acid etching depends on the acid type. HF - etching results in higher ceramic surface roughness, compared to other acids that may be used for this purpose [42][43][44][45]. A scanning electron microscope analysis of Della Bona and Anusavice [43] has shown that ceramic surface etched with 4% acidulated phosphate fluoride for 2 min was covered with precipitates, grooves could be detected after using ammonium bifluoride (1 min), while irregular etching pattern with pores as characteristic topographic feature was observed when the surface was treated with 9.6% hydrofluoric acid for 2 minutes. Etching the feldspathic porcelain with APF for 10 min resulted in shallow patterns, compared to deep channels, pores and precipitates formed by HF etching for 1 min; larger and deeper channels have been created when the HF - etching time was increased up to 4 min [44]. An insignificant effect of APF may be explained by low concentrations of hydrofluoric acid and available fluoride ions [43][45]. However, when the application time of 1.23% APF gel (clinically used as a topical fluoride for reduction of the incidence and progress of caries) was prolonged up to 60 min, increasing in surface roughness was detected, with numerous pores and deposits of particles in the form of precipitate or degradation material in the glassy matrix [46].

According to Kato et al. [47] the strongest immediate bond was achieved by etching of the feldspathic porcelain surface with HF acid (23.7 MPa); when using a solution of sulfuric and hydrofluoric acid (SHF) the bond strength was 21.3 MPa, while it was significantly lower when etching with ammonium hydrogen bifluoride (18.4 MPa). The weakest bond was built with phosphoric acid used as an etching agent. Significant reduction in bond strength after thermocycling was observed for all acids, although the HF - and SHF - treated groups exhibited bond strengths greater than 15 MPa [47]. When the etching time with 1.23% APF gel of the leucite - reinforced ceramic was prolonged up to 10 min, shear bond strength value was not significantly different to that after etching with 9.6% HF acid for 4 minutes (17.33 MPa and 17.64 MPa respectively) [48].

Acid concentration: An effect of acid etching depends not only on the acid type, but on its concentration as well. An increase in HF acid concentration increases the microroughness of the ceramic surface [49]. Uniform crystal structure is observed as a result of a dissolving of the glassy phase when the treatment is performed by HF acid with higher concentration (52%), whereas an amorphous structure expressing large porosity can be detected when etching with lower concentration (20%), when more of the crystalline phase has been dissolved [50].

Ceramic's bi-axial flexure strength after surface etching depends on the HF acid concentration. When HF etching of low fusing feldspathic porcelain was conducted during 45 or 90 s, the mean value for bi-axial flexure strength was not significantly reduced when increasing HF acid concentration from 5 to 10%. Increasing the acid concentration to 20% resulted in a significant decrease in the strength for the both etching periods. However, an acid concentration (5, 10 or 20%) had no significant effect on reduction of the bi-axial flexure strength when the etching period was prolonged to 180 s [49].

Etching time: The etching time of hydrofluoric acid affects the expressiveness of micro - morphological changes and microroughness of the ceramic surface [49]: extending the etching time, increases the depth of the pores.

According to Wolf et al. [51], the longer the action of the acid is, the rougher the ceramic surface is; anyway, etching longer than 60 s increases the occurrence of cohesive failures in the ceramic material. A SEM analysis confirmed minor changes in the structure when etching the ceramic surface between 20 and 60 s; prolonged acid etching between 90 and 180 s resulted in a more pronounced surface morphology with protruded lithium disilicate crystals [52]. Bajraktarova Valjakova [36] had found more pronounced etching pattern when the etching time was prolonged from 20 up to 120 seconds. A difference in micro-morphology was not observed when the acid etching time was extended from 20 to 30 s; prolonged etching up to 90 and 120 s caused a visible change and emphasising of the surface micromorphology. The pores and grooves in feldspar - based and leucite-reinforced ceramics became deeper; lithium disilicate - and lithium silicate - crystals became more protruded as a result of increased dissolving of the surrounding silica matrix. Prolonged etching of polymer - infiltrated ceramic network material resulted in the significant dissolving of the ceramic network [36].

Increased surface roughness and resin - ceramic bond strength were noted when increasing the etching time up to 120 s when treating feldspar - based ceramic Vita Mark II; however, prolonged etching of 180 s hurt the bond strength [53]. Nagayassu et al. [54] detected the negative effect of long-term (4 min) HF etching over the resin -ceramic bond. According to Zogheib et al. [52] prolonging the etching time increases the average roughness of the treated surface, but at the same time slightly reduces the flexural strength of the IPS e.max CAD ceramic. However, when the etching time was increased from 45 to 90 and 180 s, bi - axial flexure strength values of feldspathic porcelain were not significantly different when using 5% HF acid [49].

Ceramic type: Different ceramics expressed different surface pattern when acid - etched under the same conditions; surface etching of feldspar-based ceramic for 5 min produces pores of 5 - 7 μm depth, while 5 min etching of the glass ceramic increases the pores depth up to 10 μm [28]. According to Kim et al. [55] the effect of the surface treatment primarily depends on the chemical composition of the ceramic; hydrofluoric acid etching is the most appropriate treatment of a lithium disilicate ceramic, while tribochemical silica coating has a positive impact on the bond of luting composite to aluminum oxide and zirconium oxide ceramics. According to Valandro et al. [56], HF acid is not useful in the treatment of ceramics with a polycrystalline structure. The surface of the leucite-reinforced ceramic, after HF etching, gets a honeycomb appearance, while exposure of crystals is observed after etching of the lithium disilicate ceramic [9].

The effect of hydrofluoric acid etching on the micro-morphology of various types of glassy ceramics is not the same and depends not only on their chemical composition but the structural molecular arrangement as well. Feldspathic VITA Mark II compared to leucite-reinforced IPS Empress CAD, as well as lithium disilicate IPS e.max CAD and zirconia-reinforced lithium silicate Celtra Duo, have a similar chemical composition and percentage contribution of components, but surfaces get different etching pattern as a result of the different molecular distribution. According to manufacturers' official documents, silica and alumina contribution (in the abovementioned ceramics) is as follows: SiO_2: 56 -64%, 60 - 65%, 57 - 80%, 56 - 64%; Al_2O_3: 20 - 23%, 16 - 20%, 5%, and 4% respectively. It may be noted that all glassy ceramics have almost identical content of silicon dioxide - about 60%, while the presence of aluminium oxide is similar between feldspar - based and leucite-reinforced ceramics - about 20%, and between lithium disilicate and zirconia-reinforced lithium silicate - about 4%. However, the specific internal structure and presence of other oxides, influence the effect of HF acid etching. According to Bajraktarova-Valjakova et al. [36] numerous micropores and channels of different sizes with irregular ceramic particles can be observed on the surface of VITA Mark II; the etching surface of IPS Empress CAD gets honeycomb-like appearance, while numerous elongated or bean-like crystals have been extruded as a result of silica - matrix dissolving after etching of IPS e.max CAD and Celtra Duo respectively. HF etching of VITA Enamic causes dissolving of the superficial ceramic network, so that acrylic polymer network became visible with scattered irregular ceramic particles [36].

Hydrofluoric acid etching has no effect on the so-called polycrystalline ceramics; such are aluminium trioxide [57] [58] and zirconium dioxide partially stabilized with yttrium oxide [59]. Increase in mechanical strength by increasing the number of crystals and reducing the content of glass (silicon dioxide), leads to the creation of acid - resistant ceramics (non - etchable). Treatment with any acid will not induce any satisfactory (microretentive) changes to the surface micro - morphology to ensure proper bonding of composite cement [9] [25] [45] [60] [61] [62] [63]. Surface treatment of such ceramic restorations is performed using other methods: tribochemical silica coating [12] [13] [16], chemical treatment with methacryloyloxydecyl dihydrogen phosphate (MDP) - containing primers [13], or alternative methods [15] [16] [17] [18] [19] [20].

In conclusion, there are various methods that can be used for the treatment of ceramic bonding surface when adhesive luting is recommended. Undoubtedly, the most appropriate treatment method for silica-based ceramics is acid etching. Expressed

microroughness, and microretentive pattern that is achieved by etching with hydrofluoric acid, ensure long-term bond between luting composites and ceramic materials.

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Diabetics Retinopathy Knowledge and Awareness Assessment among the Type 2 Diabetics

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Keywords: DR; Diabetes Retinopathy; Awareness; Type 2 Diabetes

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Abstract

INTRODUCTION: Diabetic retinopathy (DR) is a leading cause of blindness worldwide. In Saudi Arabia and other Arab countries, several studies estimated the prevalence of DR ranging from 30 - 40%.

AIM: To assess the DR knowledge and its association with diabetes control among Type 2 diabetic patients.

METHODS: A cross-sectional study of patients with Type II diabetes (T2D) who had a routine visit to the endocrine clinic to assess the DR knowledge and its relation to the glycemic control. We used a questionnaire that was used in previously published studies, and the reliability was assessed using the alpha Cronbach coefficient. Patients who answered correctly > 60% were considered to have good knowledge about DR.

RESULTS: Total of 253 patients participated, 43.4% has diabetes > 10 years and 30.7% have it for 5 - 10 years, 36.4% did college degree or higher, 40.8% considered having low income. 37.7% of participants were not screened for the DR in the past year. 28.4% of participants think that seeing optometrist is enough for DR diagnosis. Diabetics with good knowledge who have T2D > 10 years were 46.3% compared to 38.6% (p = 0.04). Diabetics with good knowledge have mean A1c of 8.55 vs. 8.59 (p = 0.32), mean BMI 30.4 vs. 30.2 (p = 0.46), mean diastolic pressure was 77.12% vs. 79.48% (p = 0.03).

CONCLUSION: Almost two-thirds of screened T2D were considered to have good knowledge about DR. The good knowledge group tends to have a longer duration of T2D, more likely to have a college degree, and tend to have non -significantly better A1c control.

Introduction

The Diabetic Retinopathy (DR) is a leading cause of blindness that affects 34 million worldwide; it was estimated that it is accounting 4% of blindness cases [1]. There are several factors increase the risk of DR, the long duration of the disease, glycemic control, hypertension, hyperlipidemia, renal failure, anaemia, age, puberty and pregnancy. Furthermore, diabetic retinopathy knowledge level increases the incident of DR in young women [2]. In addition to that, some patients didn't visit the ophthalmologist for the routine annual eye exam in the past year [3][4] All of this indeed will increase the demand for better diabetes education to make T2D patients more aware about their conditions and related complication.

Patient awareness to DR will be the key to further improvements in DR management and prevention. Patients should be informed that they play an integral role in their glycemic control and eye care. There is a lack of studies to assess the level of knowledge about DR among T2D patients and find associated factors with low DR awareness in Saudi Arabia.

The primary goal of this study is to assess the DR knowledge and its association with diabetes control among Type 2 diabetic patients.

Material and Method

A cross-sectional study was conducted between August 2014 until September 2015 at King Abdulaziz Specialized Hospital, Division of Endocrinology, Taif city, Saudi Arabia. The minimum recommended sample size is 280 for 95% confidence level with 5% margin error. It is calculated based on diabetic retinopathy awareness prevalence from the previous study that shows 76% of diabetic patients aware of poorly controlled diabetes lead to retinopathy

and the diabetic population in Taif city approximately is 66797.

The study included 253 male and female with T2D who were 18 years or older and who were willing to participate. We excluded patients with type I diabetes and patients with gestational diabetes. Data were collected through a formal interview and help educated patients to obtain self - report survey. The socioeconomic data; duration of diabetes, type of medication, marital status, education level, income, smoking, physical exercise, T2D duration and Education level eye problem due to diabetes, family history of eye disease related to diabetes were self - reported. Baseline characteristics and measurements such as blood pressure, height and body weight were obtained at the time of visit. Laboratory data were collected from patient's Electronic Medical Record (EMR).

This cross-sectional study used interview-administered questionnaires that were used in previously published studies [5]. The questionnaire composite of 10 questions: 3 of them about diabetic retinopathy knowledge, 5 questions about screening and 2 of them about prevention and treatment (Table 1). It was also translated into the Arabic language. The Arabic version of the questionnaires has been used to break the language barriers and understanding among some patients. In addition to that reliability of questions was assessed using the alpha Cronbach coefficient which was 0.6 which consider acceptable. Questions consist of 10 items that aim to assess the DR knowledge and awareness. The questions are listed in Table 1. Patients who answered > 60% of the questions correctly were considered to have good knowledge about DR.

Table 1: Knowledge and Awareness Questionnaire of Diabetic Retinopathy

Knowledge and Awareness Questionnaire		
Do you think there is a relationship between retinopathy and DM?	Yes	No
Do you think diabetes mellitus may lead to blindness?	Yes	No
Have your eyes been checked by a doctor last year?	Yes	No
No need for the regular screen for DR if both eyes are good.	Yes	No
Do you think a good control of Diabetes might prevent DR?	Yes	No
Can a diabetic patient have eye problems at the same time of Diabetes diagnosis?	Yes	No
How frequently should a person with diabetes undergo an eye checkup?	- Every 6 months - Yearly or every 2 years - Only when vision affected	
When you have diabetes at the first time, you must screen your eye.	- At the time of diabetes diagnosis - 5 years after diabetes diagnosis - only if there are eye symptoms	
Do you think retinopathy is a treatable condition?	Yes	No
Do you think seeing optometrist (regular eyeglass store) is enough for people with diabetes?	Yes	No

All data were collected and analysed using IBM SPSS Statistics version 20. We used frequency for categorical variables and mean and the standard deviation (SD) for continuous variables. The Chi-squared test was used to study the relationship between nominal variables and t-test and one-way ANOVA was used to compare means. Correlation bivariate was used to assess significant between two continuous variables.

Results

Total of 253 patients was enrolled in this study with127 (50.4%) were male, mean age 52.6 ± 12.9 years old, 109 (43.4%) have diabetes > 10 years, and 77 (30.7%) have it for 5 - 10 years. 96 (37.9%) were on oral medications alone, 103 (40.7%) were on insulin alone. 165 (83.8%) were married, 159 (63.3%) did high school or less, 102 (40.8%) considered to have low income. 34 (14.3%) were actively smoker, and 40 (16.8%) reports regular exercise.

The mean A1c was 8.5%, mean BMI of 30.3 kg/m^2, 169 (71%) were considered to have uncontrolled hypertension at baseline, 39 (16%) reports they have eye problem related to diabetes, and 89 (36.6%) reports family history of eye disease related to diabetes (Table 2).

Table 2: Baseline characteristics for the whole cohort

Variables	Category	
Mean Age year (SD)	52.61 (12.91)	
Gender (%)	Male	127 (50.4%)
	Female	12 (49.6%)
Duration of diabetes (%)	Less than 5 years	65 (25.9)
	In 5-10 years	77 (30.7)
	More than10 years	109 (43.4)
Type of medication (%)	Tablet	96 (37.9)
	Insulin	103 (40.7)
	Tablet and insulin	54 (21.3)
Mean BMI (SD)	30.3 (4.7)	
Mean HbA1c (SD)	8.5 (1.5)	
Mean Blood pressure systolic (SD)	142 (17)	
Mean Blood pressure diastolic (SD)	77.9 (8.8)	
Regular exercise (%)	40 (16.8)	
Smoking (%)	34 (14.3)	
Control of blood glucose	Controlled	69 (29)
Martial state (%)	- Single	- 18 (9.1)
	- Married	- 165 (83.8)
	- Divorced	- 4 (2)
	- Widow	- 10 (5.1)
Education level (%)	- Post graduated	- 9 (3.6)
	- Graduated	- 83 (32.8)
	- High school or less	- 159 (63.3)
Income (%)	- 5000 or below	- 102 (40.8)
	- 5000-15000	- 127 (50.8)
	- More than 15000	- 21 (8.4)
Eye problem due to diabetes (%)	39 (16)	
The family history of eye disease related to diabetes (%)	89 (36.9)	

A group of 160 (64%) of screened T2D patients considered as aware of retinopathy. The mean correctly answered questions were 5.98 out of ten. More than 75% believed that T2D could cause retinopathy, which may get complicated by blindness as well as that good control of blood glucose could prevent retinopathy.

More than 60% reports had dilated eye examination, and they were significantly more likely to believe that there is a treatment for DR compared to those who had no eye examination. Around 50% were not aware of the recommendation for the DR annual screening and thought there is no need for it unless symptomatic. 71 (28.4%) of the participants thought that the optometrist visit for eyeglasses could replace the ophthalmologist visit (Table 3).

Table 3: Knowledge and Awareness Questionnaire with the percentage of the correctly answered

Knowledge and Awareness Questionnaire	Correct answer	%
Do you know the relationship between retinopathy and DM?	Yes	79.5
Do you think diabetes mellitus may lead to blindness?	Yes	79.4
Have your eyes been checked by a doctor last year?	Yes	62.3
No need for the regular screen for DR if both eyes are good.	No	52
Do you think a good control of Diabetes might prevent DR?	Yes	78
Can a diabetic patient have eye problems at the same time of diabetes diagnosis?	Yes	52.3
How frequently should a person with diabetes undergo an eye checkup?	Every one or two years	24.3
When you have diabetes at the first time, you must screen your eye.	At the time of DM diagnosis	43.7
Do you think retinopathy is a treatable condition?	Yes	66.8
Do you think seeing optometrist (regular eyeglass store) is enough for people with diabetes?	No	71.6

The most likely reported barriers that prevent patients from going to the Ophthalmologist for the recommended annual DR screening were the difficulty to get an appointment and the unawareness about the possible eye complications from T2D (Figure 1).

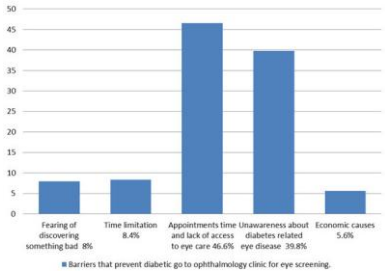

Figure 1: Barriers that may prevent people with diabetes from going to the Ophthalmology clinic for the recommended eye screening

People with diabetes with a low level of education were more likely to report that seeing the optometrist is enough for the regular eye examination (p = 0.03).

Table 4: Sociodemographic characteristic of the participants regarding awareness

Variable	Category	Aware	Not aware	P value
Mean Age year (SD)	-	52.5 (12.9)	52.7 (12.9)	.96
Gender	Male	85 (53.5)	41 (45.6)	.29
	female	74 (46.5)	49 (54.4)	
Duration of diabetes	Less than 5 years	45 (28.1)	20(22.7)	.04
		41(25.6)	34 (38.6)	
	In 5- 10 years	74 (46.3)	34 (38.6)	
	More than 10 years			
Type of medication	Tablet	63 (39.4)	33 (36.7)	.32
	Insulin	62 (38.8)	38 (42.2)	
	Tablet and insulin	35 (21.9)	19 (21.1)	
Mean BMI(SD)	-	30.4 (5)	30.2 (4.1)	.46
Mean HbA1c(SD)	-	8.55 (1.62)	8.59 (1.3)	.32
Mean Blood pressure systolic(SD)		141 (17.7)	143.8 (15)	.06
Mean Blood pressure diastolic(SD)	-	77.12 (8.8)	79.48 (8.8)	.03
Control of blood glucose.	Controlled	70 (49	34 (40.5)	.16
Regular exercise	-	29 (19.3)	11 (12.9)	.09
Smoking	-	18 (112)	16 (18.8)	.15
Marital status	Single	11 (8)	7 (12.3)	.22
	Married	117 (85.4)	45(78.9)	
	Divorced	2 (1.5)	2 (3.5)	
	Widow	7 (5.1)	3 (5.3)	
Education level	Post graduated	9 (5.6)	0	.007
	Graduated	57 (35.6)	25(28.4)	
	High school or less	94 (58.8)	63 (71.6)	
Income	5000 or below	63 (39.6)	36 (40.9)	.07
	5000*15000	79 (49.7)	48 (54.5)	
	>15000	17 (10.7)	4 (4.5)	
Eye problem due to diabetes.	-	29 (18.6)	10 (11.8)	.18
Family history of eye disease related to diabetes.	-	56 (36.1)	33 (38.8)	.61

The aware group was significantly more likely to have higher school educational level (p = 0.007), longer duration of diabetes (p = 0.04), and lower mean diastolic blood pressure (p = 0.03). There was no significant difference between both groups in regards to age, lifestyle habits, income, or the family or the personal history of eye disease related to diabetes (Table 4).

Discussion

The Global prevalence of DR among diabetic patients is estimated to be 34.6% [6]. In the Eastern region of Saudi, the prevalence of DR was 30% [7]. More than 12% of who is suffering from DR for 30 years or more are blind [1].The pathogenesis of DR is multifactorial but is primarily due to the metabolic effects of chronic hyperglycemia, which result in dramatic vascular changes and subsequently leads to retinal injury and ischemia [4]. The vast majority of patients who develop DR have no symptoms until the very late stages by which time it may be too late for effective treatment [8][9][10]. Proliferative retinopathy incident was more likely associated with less educated women. American Diabetes Association (ADA) guidelines recommend screening for retinopathy at the time of diagnosis T2D then annually after that [11].

In our study, 64% of the screened T2D found to be aware of DR. This awareness correlated with patient's educational level as most of our patients who report low education level have low DR awareness score. Some of the previously published studies reported that DR knowledge and awareness is poor among the T2D [10] [12] [13] [14]. However, it is difficult to compare our results with other as most of the published studies used different instruments to assess the DR knowledge among those patients. However, in Saudi Arabia and other Arab countries, several studies have estimated the prevalence of DR ranging from 30 - 40%, and there is a steady increase in the number of cases discovered which emphasise on the importance of awareness about diabetes and its complication [12] [13] [15].

It has been previously shown by different studies that diabetic control among type 2 diabetics are generally poor which ultimately resulting in a high rate of complications [14] [16] [14]. In our study, half of the patients were poorly controlled diabetics, and the mean A1c was 8.5, and poorly controlled HbA1c can contribute to the development of DR as well as the other complications. Interestingly, we noticed that patients with high HbA1c they were non - significantly less likely to be aware that those with more controlled HbA1c. Also BMI, age and gender were not

significantly different between groups. A study conducted in Turkey showed that patients who had T2D for more than 10 years were more likely to be aware of diabetic retinopathy [17]. Similarly, in our study diabetics with T2D for more than 10 years were more likely to be aware and more likely to have a regular eyes check-up annually. In our study, we found that 28.4% of the participants think that seeing an optometrist is enough for diabetics and that was closely related to patient's level of education. Nonetheless, 37.7% of the participants do not attend a routine eye exam furthermore; one of the most reasons reported by participants for not attending regular eye examinations was appointment time then followed by lack of awareness about DR. Even in some countries where you find high level of awareness about diabetic retinopathy, people with diabetes still do not visit ophthalmology clinics for the recommended routine eye examinations on a regular basis. A Japanese study showed that more than 98% of patients were aware of DR, but only 69.5% of the patients visited the ophthalmologist routinely on a regular basis [18]. This could be explained by a gap between the level of awareness and practice among people with diabetes and that is why focusing in knowledge alone is not sufficient in health awareness, it should be along with behavioural practice to make dramatic changes in improving patient's compliance and self -care.

Our study limitations were that our study was a single centre and our sample size is slightly under recommended sample size. Study strengths, participants were interviewed and helped by our researchers at specialised Endocrinology clinic and using a score that represents a sum of questions related to DR rather than using the single question to decide awareness status.

In conclusion, almost two third of screened T2D were considered to have good knowledge about DR. The good knowledge group tends to have a longer duration of T2D, more likely to have a college degree, and tend to have non - significantly better A1c control.

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Dyspnea in Children as a Symptom of Acute Respiratory Tract Infections and Antibiotic Prescribing

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Abstract

BACKGROUND: Dyspnea is an unpleasant feeling of breathing difficulty, shortness of breath and inability to satisfy the hunger for air. The role of family physicians is to be prepared to recognise dyspnea as a symptom of acute respiratory infections (ARI), to perform triage and managing of children with acute dyspnea and make continuous education of parents. In the treatment of acute dyspnea more important is to treat dyspnea as a symptom than the prescribing of antibiotics (AB). Nowadays, even more often large amount of children, because of the noncompliance in the treatment and the pressure from the parents, unnecessary is hospitalised and frequently used antibiotics: According to the guidelines, a small percentage of children with ARI should be treated with AB. The rate of antibiotic prescription should be around 15-20% and lower.

AIM: To assess doctor's AB prescriptions in Primary care practices in Macedonia, for ARI and dyspnea in children we use the data from a National project about antibiotic prescribing for acute respiratory tract infections, which has been run in 2014 November as a part of E - quality program.

METHODS: Eighty-six general practitioners from Macedonia have taken participation in it. The group of 3026 children, from 0-5 years of age, with symptoms of dyspnea, was analysed. We have found a rate of 54.6% antibiotic prescriptions (AB). From 3026 children with dyspnea, AB got 1519 children, 852 of which were prescribed by a specialist.

RESULTS: The children were mostly diagnosed with upper ARI, in 57.7%. The most used AB is amoxicillin + clavulonic acid. We concluded that there was an increased and inappropriate prescribing of antibiotics in children with ARI, presented with dyspnea in Macedonia.

CONCLUSION: Perceptions and the parent's attitudes do not correlate with the severity of clinical picture of the disease in children and lack of use Evidence-based medicine (EBM), insecurity, fear, loss of patients effect on antibiotic prescribing of the doctors.

Introduction

Dyspnea is an inability to satisfy the hunger for air and leads to increased activity of the respiratory muscles, stimulation of neurotransmitter receptors and increased pCO2 concentration**.** The most frequent aetiology for dyspnea in children are acute respiratory infections (ARI) and other diseases, such as asthma triggered by viruses, enlarged tonsils, allergic rhinitis, foreign body aspiration and other less frequent diseases, such as large tongue, choanal atresia, tracheomalacia, cystic fibrosis, bronchiectasis, dysfunction of the vocal cords, bronchial atresia, chest wall diseases, chest deformations, weakness of the respiratory muscles etc**.** However, some of these can rapidly become life-threatening and therefore require rapid pre-hospital management [1]**.** Dyspnea is recognized by physical examination of the child and manifested with different severities of signs such as: child taking special sitting position that allows him an easier breathing , stridor, stertor (obstruction of the level of pharynx), increased body temperature, coughing, inter/subcostal retractions, wheezing, moaning, cyanosis [2]**.** In acute dyspnoic children, assessment of dyspnea severity and treatment response is frequently based on clinical dyspnea scores [3]**.** The role of family physicians is to be prepared to recognise and manage children with dyspnea**.** Therefore, using an algorithm for

assessment of stridor and bronchospasm could be helpful. Also, they should make continuous education of parents to change their attitudes and overcome prejudices. Because of the noncompliance in treatment, lack of use of Evidence-based medicine (EBM), lack of time, doctors fear of complications, diagnostic insecurity, the pressure from parents, tradition of uncontrolled use of antibiotics (AB) and the connotation that AB is for all diseases, a large number of children with dyspnea and acute ARI unnecessary are hospitalized and frequently used antibiotics [4]. Use of AB for dyspnea in most of the cases is ineffective and inappropriate. The rate of antibiotic prescriptions should be around 15-20% and lower [5]. Necessary and beneficial treatment with AB is needed only for acute tonsillopharyngitis caused by Group A beta-hemolytic streptococcus (GAS), bacterial tracheitis and pneumonia**.** The use of the guidelines plays a big role in helping physicians to manage children with dyspnea better and avoid unnecessary AB prescribing [6]. The most important thing for the doctors is to recognise urgent life-threatening symptoms of acute dyspnea, to be skilled in performing CPR, and determine the number of respirations, O2 saturation with a pulse oximeter, to organise quick and safe referral [7]. Dyspnea and stertor are connected with large tonsils and needs a consultation with ENT specialist. Dyspnea, agitation and drooling are symptoms of the epiglottis and need securing airways and referral**.** Dyspnea and stridor are the signs of laryngitis and ambulatory treatment of mild and moderate laryngitis with oral or intramuscular Dexamethasone, or inhaled Budesonide is useful [8]**.** Dyspnea, intoxication and fever associated with bacterial tracheitis need securing airways and referral. Dyspnea and wheezing in children > 2 years with a history of paroxysmal coughing associated with childhood asthma. A lot of children with asthma are mostly not recognised and are prescribed a lot of AB [9] [10]. Children < 2years with a dry cough, fever, nose secretion, crepitation and wheezing are associated with bronchiolitis**.** Dyspnea, cough, fever or moaning, choking and increased respiration, are signs of pneumonia. Mild or moderate pneumonia can be treated ambulatory with antibiotics and follow up. AB of the first choice is Amoxicillin. There is no need for making a chest x-ray (except for children < 2months, if there is no improvement after treatment or in recurrent pneumonia) [11].

Material and Methods

We used the data from the National project about antibiotic prescribing for ARI run in November 2014, as a part of E - quality program, supported by International Primary Care Respiratory Group (IPCRG). 86 general practitioners from different areas of the Republic of Macedonia took part in the project. Both written informed consent from each doctor and verbal informed consent from every patient or parent were obtained, before fulfilling the project questionnaires. Socio-demographic and medical data were obtained using personal or parental interviews. A group of 3036 children, from 0-5 y old, presented with symptoms of dyspnea, was analysed.

The obtained data were analysed by using STATISTICA for Windows version 7.

Results

A total number of 3036 children from 0-5 years old, presented with dyspnea as a symptom of ARI were analysed, (Min. 0.1, Max. 5, Mean 2.57, St. Deviation 2.33).

Our analysis has shown that 63.8% of children with dyspnea were taken to the doctor's office, after day 2 of symptoms. Anamnestic data of an average duration of symptoms is 3.5 days without AB and 4 days with AB. In the first visit, there were 2412 children, 1228 of them got an AB, of whom only 59 children got an AB under the pressure of parents? The leading symptoms in the first 3 days are: coughing 69.6%, runny nose 46.3%, fever 40.3%, swallowing difficulties 16.3%, stuffed nose 22.6% and sore throat 11.1%. Control checkups were made in the case of 581 children, 308 of them received AB, and only 4 children got an AB under the pressure of parents. Average symptoms duration in 308 children was 5.5 days. After 4 days the leading symptoms were: coughing 73.5%, running nose 42%, increased temperature 36%, wheezing 16.5%, expectoration of sputum 15.7%, and difficulties in breathing 10.3%.

The rate of AB prescriptions for ARI presented with dyspnea in children is 54.6%, 3.16 % of the data were irrelevant due to improper fulfilling. From 3036 children presented with dyspnea, 1519 children got AB, 852 of which from a specialist (56%). Only 140 children had a complication (9.2%). 63.8% of children with dyspnea were taken to the doctor's offices after day 2. The children with ARI who were presented with dyspnea after physical examination were diagnosed mostly like upper ARI: acute rhinitis, pharyngitis, tonsillitis, streptococcal tonsillitis, laryngitis, croup and epiglottitis (J00, J02, J03, J03.0, J04) in 57.7 %. The children with lower ARI were diagnosed with acute bronchitis (J20) in 19.3%, tracheitis 2.25%, bronchiolitis 3.73%, pneumonia 3.21%. The percentage of complications needed antibiotic treatment was 9.2%. The data also showed that, the most prescribed antibiotic for dyspnea in children is amoxicillin + clavulonic acid 29.69%, amoxicillin 26.33%, Penicillin G 3.88%, cephalosporin's first and second generation 23.37%, cephalosporin's third generation 2.76%, macrolides

6.25%, ampule therapy 3.09%, unknown antibiotics 1.18%, aminoglycosides 0.33%.1968 children were presented as upper respiratory tract infection, and 1047 of them received antibiotic (35.6% of total patients), only 962 are presented as low ARI, of whom 557 (18.9% of total patients) were given AB. 54.6% of all children presented with dyspnea as a symptom of ARI received AB, 45.5% did not receive any. In both groups we found increased AB prescribing.

Table 1: Gender, parents' educational level, low and upper ARI are among children with dyspnea who did or did not receive antibiotics

Characteristics	N/% of children with dyspnea and without AB	p*	N/% of children with dyspnea and with AB
Girls	596 (21.09%)		751(26.58%)
Boys	728 (25.76%)	0.008	751(26.58%)
Mothers' educational level:			
Primary school	282 (21.28%)	0.014	421 (31.77 %)
Secondary school	615 (33.01%)	0.78	626 (33.60%)
University degree	304 (16.32%)		318 (17.07%)
Fathers' educational level:			
Primary school	246 (21.77%)	0.13	327 (28.94%)
Secondary school	731 (35.49%)	0.61	772 (35.49%)
University degree	264 12.82%		293 (14.22%)
Lower ARI	557 (18.95%)		415 (33.06%)
Upper ARI	1047 (35.6%)	0.036	921 (31.32%)
Attending daycare	420 (15.78%)		510 (19.17%)
Not attending day care	814 (30.59%)	0.358	917 (34.46%)

*X^2-test.

The results show significantly increased prescribing of AB in children with dyspnea in the group of mothers with primary education level and the group of children with upper ARI. In the group of children with upper ARI, we found significant increased AB prescribing as compared with children with low ARI ($p < 0.05$). Boys more frequently have dyspnea and significantly use more AB, then girls. There are no significant differences in prescribing of AB in children with dyspnea in the groups of mothers with secondary education level and the ones with the university degree. Attendances of a daycare centre have no significant influence on AB prescribing in children with dyspnea (Table1).

Table 2: Dyspnea in children with ARI and Spearman rank correlation (R)

Variable	Variable	Spearman rank correlation (R)	P<0.05
Dyspnea	Age of children	0.056	0.002
Dyspnea	Education of the mothers	0.130	0.00
Dyspnea	Asthma	0.2135	0.00
Dyspnea	Coughing	0.069	0.00
Dyspnea	Prolonged inspiration	0.075	0.00
Dyspnea	Wheezing	0.5238	0.00
dyspnea	Use of bronchodilators (relievers)	0.334	0.00
Referral to specialist	Antibiotic prescribing	0.065	0.00

Statistical analysis of Spearman Rank Correlation (R) shows a significant correlation ($p < 0.05$) between dyspnea and age, educational level of the mothers, the presence of asthma, symptoms of coughing, stridor, wheezing and the use of bronchodilators and strong correlation between referral to a specialist and antibiotic prescribing. Visits to a daycare centre haven't got a significant impact on antibiotic prescribing (Table 2).

Discussion

The most predominant reasons for dyspnea are ARI in children, coming with different severities and treatment. The most of those diseases should not be treated with antibiotics [12]. The rate of AB prescription in Macedonia is higher and inappropriate than in the countries of northern Europe and does not comply with EBM [5]. The most of the children were taken to the doctor's office after the second day of the disease and received AB, even though most of them (> 80%) had virus upper ARI and mostly didn't have the benefit of it. The symptoms last for 3.5 - 4 days with or without AB, but the parents have a fear of complications and lack of medical education [13]. Even the percentage of complications is low and small number of children got an AB under the pressure of parents(which counts low and unusual), the most of the children received AB after the first visit, bring to conclusion that the doctors prescribe more AB than the willingness of the parents to receive antibiotics [14]. The possible reasons for that are as follows: fear of complications, easy approach of the parents to the specialists for minor diseases especially for the children, lack of parent's education and [15]. The results showed increased AB prescriptions in children with upper ARI and lowered ARI by GP,s and specialist in the hospitals even though most of them, according to guidelines and EBM didn't need AB treatment [13]. Increased AB prescriptions appear in both groups, especially in the one with upper ARI even when the doctors know to recognise the aetiology of dyspnea [16]. The main reasons for that are the doctor's and parent's attitudes [17] [18]. The parents have not been properly educated and prepared to be able to recognise dyspnea in children and often have fears which do not help to develop a critical attitude. They strongly believe in the effectiveness of various AB, thinking that AB is a cure for treatment of all diseases and make a strong pressure to the doctors' decision making, which in fact is not so obvious , but just their mere attitude and the filling of parent's fear can effect on the doctors' decision to prescribe AB [18]. Under that kind of pressure, fear of complications, uncertainty in diagnosis and willingness to protect themselves by law, doctors unnecessary prescribe an AB. According to the results, doctors rather then the parents are more likely want to prescribe AB, even though they have made a true diagnose and know that there is no need for an AB [4] [19]. The results of use bronchodilators indicated that doctors have excellent diagnostic abilities and can recognise and treat symptoms of dyspnea in children [20]. Boys with ARI are more predisposed to dyspnea then girls and

received more AB; perhaps this is in correlation with the structural differences between boys and girls similar to the Croatian study results [21]. Education of the mothers has a significant influence on AB prescribing only in the group of the mothers with primary educational level. We also found a statistically significant correlation between AB prescribing for dyspnea and referral to a specialist. There is no significant difference in the rate of prescribing AB between the groups of children who are attending or not attending in the daycare centres [21].

We can conclude that there is an increased and inappropriate prescribing of AB in children 0-5 years old with ARI presented with dyspnea in Macedonia. Dyspnea in ARI is significantly in correlation with the age of the children from 0-5 years old, the primary level of mother's education, wheezing, coughing, prolonged inspiration, asthma and the use of bronchodilators. The majority of the children presented with dyspnea are diagnosed mostly as upper respiratory tract infections. Perceptions and the parent's attitudes don't correlate with the severity of the clinical picture of the disease in children. The specialists also prescribed a lot of AB. Possible reasons for increased AB prescribing for dyspnea in ARI by the doctors in Primary health care practices are as follows: insufficient use of EBM, doctor's fears of complications, burning out, overload of patients, lack of time, need to meet the parent's demands, unmotivated, with no reward. On the other side, parents have high expectations and requirements, insufficient education, fears, prejudices and misconception. This conclusion can and should raise the need to implement new strategies in term of changing attitudes of both, doctors and parents.

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Body Weight Concern and Belief among Adolescent Egyptian Girls

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Abstract

BACKGROUND: Body weight concern and belief in adolescent females are of great importance. They are the keys to successful dietary interventions including dietary habits' modifications to practice a healthy diet. This critical phase of transition from childhood to adulthood is the most sensitive stage of behavioural rectification.

AIM: This study was conducted with the aim to figure out the prevalence of body image dissatisfaction and the association of body image satisfaction and believe with body mass index in adolescent girls aged 16-18 years.

MATERIAL AND METHODS: Two hundred and three Egyptian adolescent females were enrolled in this cross-sectional study. Their mean age was (17.4 ± 0.64) years old. Self-administered questionnaires about the students' body satisfaction and weight belief were answered by the candidates. Their body mass index was calculated. Also, sociodemographic data were collected. Data were analysed using SPSS software version 16.0. Chi-square test was conducted for the variables.

RESULTS: Sixty-eight percent of the students were within normal weight, 3.3% were underweight, while 18.2% and 10.5% were overweight and obese respectively. Body dissatisfaction was prevalent among 37.4%. The prevalence of body dissatisfaction was higher in both obese and underweight candidates reaching (93.8% and 80%) respectively. This reflects students' awareness of their body shape.

CONCLUSION: More than one-third of adolescent females were dissatisfied with their body image. The subjective belief about self-body image matched the objective Body Mass Index measurements.

Introduction

The prevalence of overweight and obesity in the Middle East has been estimated to be the second in the world, after North America [1]**.** Obesity has become a problem of concern worldwide [2]**.** Adolescent obesity is a public health problem and is one of the major health challenges of the 21st century [3]**.**

Obesity is highly associated with eating disorders, which include disturbed eating attitudes, body weight concern, dieting, anorexia nervosa and bulimia [4].

In the Eastern Mediterranean Region (EMR) and Arab societies, plumpness counted to be a desirable feminine trait. On the other hand, the up to date EMR researchers showed an increased westernised vision of perfect body shape [5]**,** where slimness is a sign of female beauty [6]. This mismatch of cultures caused by the intrusion of western ideas could increment the worries about body shape. Body image concern is defined as the degree of satisfaction about oneself as regards size, shape, and general appearance [7]**.**

The relatives, the media, the colleagues and the community all have an impact on body shape satisfaction. But the greatest influence is that of the media and the community through standardising a "thin ideal" for female beauty and a "muscular sportive shape" for males [8]**.**

The abnormally high ranges of BMI are accompanied with unsatisfaction about oneself body

image [9], the same thing with swings of weight [10] especially among females [11]**.** Body image unsatisfaction is mostly encountered in the period of adolescence [12]. Worries about oneself silhouette are associated with eating disorders and loss of self - confidence [13]. A study conducted on undergraduate students at Assuit University in Egypt found that 40% of the female students and 25.6% of male students having mild to marked body image concern [14].

Sparse studies on body image concern among young adults and adolescents in Egypt are limited which justify the present study. The purpose of the current study is to find out the prevalence of body image dissatisfaction and the association of body image satisfaction and belief with body mass index (BMI) in adolescent girls aged 16-18 years.

Subject and Method

A cross-sectional study included two hundred and three adolescent girls randomly selected from secondary schools in Giza governorate. The subjects were enrolled into the study according to the following inclusion/exclusion criteria:

Inclusion criteria: Female gender with age range of 16 to 18 years old.

Exclusion criteria: Male gender and age of less than 16 or more than 18 years old.

Self-administered questionnaires were answered by the participants. It included sociodemographic data as age, father and mother education, number of individuals per family, in addition to two main questions:

1. About Body Weight Satisfaction: Students were asked whether they are satisfied with their body weight, participants select one of the proposed answers (satisfied, not satisfied).

2. About Bodyweight believes: Students were asked (How do you feel about your body image?). Again the students select one of the proposed answers (thin or under-weight, normal, overweight and obese).

Questionnaires were distributed to the students and a week later, were collected. Parental consent was obtained before starting the study and participating in the study was not obligatory. The study protocol and the questionnaires were approved by the Research Ethical Committee at the National Research Center.

Anthropometric measurements

Weight and Height were measured, and calculation of the body mass index was done by the equation (BMI = Kg/m^2) and plotted on the growth charts of the Centers for Disease Control and prevention. Accordingly, BMI for age was stratified into four categories. Underweight defined by having BMI less than 5^{th} percentile. Normal weight defined by BMI ranging from the 5th percentile to less than the 85^{th} percentile. Overweight defined by BMI ranging from 85th to less than the 95^{th} percentile. Obese defined by BMI equal to or greater than the 95^{th} percentile [15]**.**

Statistical analysis

Analysis of data was performed by using Statistical Package for the Social Science SPSS version 16.G. [16]. Data were presented as a mean and standard deviation. Chi-square test was conducted for the variables and was used to detect the significant difference in the distribution between groups at P -value < 0.05.

Results

The study group consisted of two hundred and three adolescent girls with a mean age of (17.4 ± 0.6) ranging from (16-18 years old). The mean number of their families' members was (5.2 ± 1.2) individuals. As regards to parents' education and occupation, we considered the father job to reflect both education and economic status.

It was interesting that 72.9% of the fathers were highly professional. 5.9% of students' fathers were either retired or jobless or dead. Almost half of the mothers (49.8%) were housewives. Unfortunately, the day we took the anthropometric measurements there was refusal by some students of further participation, and there was also scholar absenteeism of some participants. Thus, the weight of only one hundred eighty-six participants out of two hundred and three and the height of only one hundred eighty-three participants out of two hundred and three was measured. The mean weight and the mean height were (62.4 ± 13.8 kg) and (163 ± 6.8 cm) respectively as shown in Table 1.

Table 1: Sociodemographic characteristics of the studied sample (n = 203)

Variable	Mean	Range
Age (n = 203)	17.4 ± 0.6	16-18
Weight (n = 186)	62.4 ± 13.8	41-120
Height (n = 183)	163 ± 6.8	145-187
Father job (n = 203)	Frequency	Percent
High profession	148	72.9%
Self-employed	24	11.8%
Low profession	19	9.4%
Others	12	5.9%
Mother job (n = 203)	Frequency	Percent
Working	102	50.2%
Housewife	101	49.8%

According to the body mass index categories, 3.3% of our students were underweight, 68% were normal, 18.2% were overweight, and 10.5% were obese Figure 1.

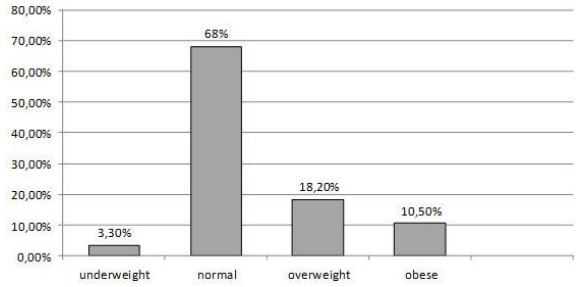

Figure 1: Distribution of BMI categories

We asked the students about their body image satisfaction and belief. Their answers revealed that 37.4% were dissatisfied and 41.4% were satisfied table 2. Since participation in the study was not obligatory, not all of the candidates answered the two main questions of the study (body satisfaction and body image concern). Those who had dropped answers were counted as missing in the data analysis.

Table 2: Body image satisfaction among students (n = 203)

Body image satisfaction	Frequency	Percent
Satisfied	84	41.4
Dissatisfied	76	37.4
Missing	43	21.2

Thirty-one percent believed to have a non-average weight, of which 11.3% believed to be thin and 19.7% believed to be fatty, Table 3.

Table 3: Weight belief among students (n = 203)

Weight belief	Frequency	Percent
Thin	23	11.3%
Average	84	41.4%
Fatty	40	19.7%
Missing	56	27.8%

After exclusion of all those who had missed values either in BMI or body image belief or satisfaction, we did cross-tabulations for BMI with body image satisfaction and body image belief, Table 4 and Table 5.

A higher percentage of those who were obese were not satisfied with their BMI, presenting 93.8% (15 out of 16 obese cases). It is worth mentioning that 80% of those who were underweight were not satisfied with their BMI, Table 4.

Table 4: Relation between BMI and body image satisfaction (n = 139)

BMI	Satisfaction		Significance
	Satisfied	Dissatisfied	
Underweight (n = 5)	1 (20%)	4 (80%)	0.00
Normal (n = 93)	61 (65.6%)	32 (34.4%)	
Overweight (n = 25)	9 (36%)	16 (64%)	
Obese (n = 16)	1 (6.2%)	15 (93.8%)	

From Table 5, we noticed that fifty-five percent of those who believed that they had a normal weight had a normal BMI. Eighty percent of those who believed being thin were truly underweight and had an abnormally low BMI. And 93.8% of the obese believed to be fatty. Thus the subjective believe about self-body image did match the objective BMI measurements in all BMI categories.

Table 5: Relation between BMI and weight belief (n = 126)

BMI	Weight belief			Significance
	Thin	Average	Fatty	
Underweight (n = 5)	4 (80%)	1 (20%)	0 (0%)	0.00
Normal (n = 85)	18 (21.2%)	55 (64.7%)	12 (14.1%)	
Overweight (n = 20)	0 (0%)	11 (55%)	9 (45%)	
Obese (n = 16)	0(0%)	1 (6.2%)	15 (93.8)	

Discussion

Adolescence is the stage of biophysical and psychosocial alterations [17] and is a vital phase for body image development due to a variety of social, cultural, physical, and psychological changes that occur between the ages of 12 years and 18 years [18].

Body image is defined subjectively by the person's satisfaction with own body measurements [19].

Young people are more prone to imitate the ideal body shape parameters. Meanwhile, those young people are in a critical stage of self-identification that is greatly influenced by accepting own physique and building self-confidence [20].

Several social, psychological and cultural factors are associated with body weight concerns [21].

The study group included two hundred and three adolescent girls attending secondary school with a mean age of (17.4 ± 0.6) ranging from 16-18 years old. This age range is matching the one found in other studies which demonstrate the high prevalence of weight dissatisfaction among adolescence [22] [23]. Father's job is considered to reflect both education and economic status of the adolescents' families; our study showed that 72.9% of the fathers were highly professional and 49.8% of their mothers were housewives. Musaiger and colleagues reported that 31.2% of the adolescents' fathers had a high level of education [24]. Socioeconomic stratification is evaluated by several parameters that differ from one study to another. Consequently, no specific association was determined between body image satisfaction and socioeconomic levels [23].

This study showed that 3.3% of the participants were underweight, 68% were normal, 18.2% were overweight, and 10.5% were obese which considered different from the prevalence of

underweight, overweight, and obesity among adolescent girls in a study conducted by Silva and colleagues, which were 23%, 10.7% and 3.6% respectively [25].

The prevalence of overweight and obesity among adolescent girls in Shandong, China in 2005 were 8.75% and 5.76% respectively [26] which are considered lower than our values.

In another study conducted by Manyanaga and colleagues, in seven African countries where Egypt was one of them, the rates of underweight, overweight and obesity among adolescents in Egypt were, 12.6%, 31.4% and 9.3% respectively [27].

Cole and colleagues developed an internationally acceptable definition of child overweight and obesity where information on body mass index was obtained from six large nationally representative cross-sectional studies on growth. The upper and lower limits are useful in comparisons between different nations as regards the distribution of overweight and obesity in paediatrics where the prevalence rate is 5-18% for overweight and 0.1-4% for obesity at 2-18 years old [28]

The results of the current study are in the international reference range regarding the rate of overweight, but the prevalence rate of obesity in our study is higher than the international reference range.

The abnormally high BMI is prevalent in Egypt during the period of adolescence, which indicates a transient change in diet due to newly acquired urban habits, [29] in addition to a rise in both social and economic levels [30]**.**

This study demonstrates the burden caused by the coexistence of obesity and underweight. It was revealed that 31% believed to have a non-average weight of which 11.3% believed to be thin and 19.7% believed to be fatty. 41.4% of our participants were satisfied with their body image, a rate similar to that found by Eduila and colleagues [23]. Those who were not satisfied with their body weight were 37.4% of the participants which agreed with the results of other studies. Al – Sabbah and colleagues reported that the prevalence of weight dissatisfaction among Palestinian females aged 12-18 years was 33.9% [22] and Musaiger had reported that 32%-39% of the participants were dissatisfied with their current weight [31].

However, Eduila and colleagues and Pelegrini and colleagues reported a higher prevalence rate of body image dissatisfaction among Brazilian adolescents (71.4%) and (61.3%) respectively especially among girls [23] [32]. These findings show that weight dissatisfaction has been increasing in prevalence worldwide.

More worries and less satisfaction about body image are found in women. As they are much more minded about slimness and much more anxious about any added weight [33]. The influence of parents and peers, exposures to mass media and pressure to be thin have been shown to be risk factors for increased body dissatisfaction [21]. In another study conducted in Egypt, it was found that women were dissatisfied with their body weight due to the influence of fashion as shown on television and in fashion magazines [34].

The study showed that a high percentage of the included adolescent girls who were obese were not satisfied with their current weight presenting 93.8%. Similarly, Goswami and Colleagues reported that overweight students had a significantly higher prevalence of dissatisfaction [35]. Also, research done in Kuwait revealed body dissatisfaction in 81% of fatty females attending the university in comparison to dissatisfaction in only 30% of their average weight peers [36]. The high prevalence of overweight and obesity is an impotent factor which contributes to body weight concern. Also, obesity was found to decrement self-body image satisfaction [37].

Our study showed that 80% of those who were underweight were not satisfied with their weight. In contrast, Goswami and Colleagues reported that underweight participants had a highly significant rate of satisfaction [35].

Results showed that 55% of those who believed that they had a normal weight had a normal BMI. 80% of those who believed being thin were truly underweight and had a low BMI, and 93.8% of those who believed being fat were obese and had a high BMI indicating that the subjective belief about self-body image matches the objective BMI measurement in all BMI categories. These results are in contrast with other researchers. The study group in a research done by Nunes and colleagues included female candidates of teenagers up to twenty-nine years old. They detected in their study, a real self-estimation of being fatty only in one third of those with a truly high BMI [38], Duong and Roberts, also found that adolescent females with normal weight had considerably high odds of perceiving themselves as overweight; [39] meanwhile Eduila and Colleagues, noticed that 64.1% of their study group were not satisfied with their body image in spite of having normal BMI. On the other hand, 29.9% were dissatisfied and were having a high BMI [23].

Results of the scientific research have pointed to the inconsistency of nutritional status and BMI as indicators of satisfaction about body image [40] therefore, weight dissatisfaction is mainly dependent on self-body image perception [22].

Thus, body dissatisfaction among adolescent girls must be considered a critical issue and must be enlisted in health problems of adolescence [32].

In conclusion, the present results conclude that the prevalence of overweight and obesity is (28.7%) and the prevalence of underweight is (3.3%), and so highlighting the existence of the double burden

of both extremes of abnormal BMI in adolescence. The prevalence of body image dissatisfaction (37.4%) is high among adolescent girls whether they were overweight or underweight. The subjective belief about self-body image matches the objective BMI measurements.

Recommendation: Body image dissatisfaction should be considered an important public-health problem that needs preventive measures providing a real reflection of cultural concepts about body image perception that may endanger health. Scholastic programs are very useful in rectifying unhealthy eating habits, in promoting exertion and in correcting body image distortion in adolescence.

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Knowledge and Awareness of Medical Practitioners of Jazan City towards Oral and Maxillofacial Surgery as a Specialty

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Keywords: Awareness; Medical practitioners; Oral and maxillofacial surgery

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Abstract

BACKGROUND: In many health services communities the scope of oral and maxillofacial surgery (OMFS) as a discipline is frequently not probably understood. Good awareness towards OMFS among different branches of health services providers is essential for better referral strategies and will be for the benefit of the patient.

MATERIALS AND METHODS: The cross-sectional study was done using a specially prepared questionnaire distributed randomly to 125 general medical practitioners working in Jazan province. In this questionnaire, there were also some close-ended questions to evaluate awareness regarding a variety of conditions treated by the oral and maxillofacial surgeons.

RESULTS: Out of 125 participants, 105 (84%) were aware of the oral and maxillofacial surgery as a speciality branch of dentistry. Only 52 (41.6%) participants were aware of the different treatment modalities coming under the scope of oral and maxillofacial surgery. Also in the referral of cases to the oral and maxillofacial surgeon, 50 (40%) participants referred their oral and maxillofacial region cases to OMS. Tooth removal was the only procedure where most of the medical practitioners knew it is a speciality procedure of the oral and maxillofacial surgeon. For facial fractures, 76 medical practitioners believe it comes under the scope of the orthopaedic surgeon. Similarly, for facial abscesses, 81 and 36 practitioners responded that it is a job of a general surgeon and OMS respectively.

CONCLUSION: There is low awareness toward the scope of oral and maxillofacial surgery in the medical community. Knowledge and awareness of the scope of oral and maxillofacial surgery can improve the success and promptness of delivery of health services.

Introduction

Oral and Maxillofacial Surgery is a speciality branch of dentistry. It functions more like a borderline between dentistry and medicine [1] [2]. Unfortunately, it has been very common to alienate Dentistry from other medical specialities. Since OMFS was a branch of dentistry, then medical practitioners link it to Dental practice or by far to no more than dentoalveolar procedures.

Oral and maxillofacial surgery had expanded with time to include cases of facial trauma, jaw pathologies, dentofacial deformities, temporomandibular joint disorders, salivary gland pathologies, trigeminal neuralgias, orofacial pains, swellings of the face and neck and oral cancer [2].

New methods had also been introduced in the field like distraction osteogenesis, tissue engineering, dental implant surgeries, treatment of cleft lip and palate, and reconstruction, etc. However, still, it is not clear how OMFS is being perceived as a speciality among medical professionals [2].

In contrast to common belief, the work of an oral and maxillofacial surgeon (OMS) does not start and end with teeth and its surroundings. It also expands to include procedures that enhance the quality of life by providing better function and

aesthetics, as well as life - saving procedures. In many countries, OMFS as a speciality is not developed in the thoughts of medical professionals and the general public [3].

In Saudi Arabia, the general perception towards OMFS does not differ much from what is noticed in many countries, but this was a personal opinion which is not supported by any studies.

This study was done to assess the knowledge and awareness of general medical practitioners towards oral and maxillofacial surgery as a speciality.

Materials and Methods

The cross-sectional study of knowledge and awareness towards oral and maxillofacial surgery as a speciality was done using specially prepared questionnaire. The questionnaire was validated by a pilot study. Also, some closed-ended questions were formulated for the evaluation of a variety of conditions treated by the oral and maxillofacial surgeons. The questionnaire was distributed randomly to 125 medical professionals working in Jazan province. Approval from college level ethical committee & informed consent from each of the participant were taken. All the data were collected, and statistical analysis was done.

Results

Out of 125 participants, 55 were male, and 70 were females. The participants were from different medical specialities such as general practitioners, family medicine, obstetrics and gynaecology, medical interns, etc. The clinical experiences of the medical practitioners ranged from 1 to 15 years.

Out of 125 participants, 105 (84%) were aware of the oral and maxillofacial surgery as a speciality branch of dentistry. Only 52 (41.6%) participants were aware of the different treatment modalities coming under oral and maxillofacial surgery. Also in case of referral of cases to the oral surgeon, 50 (40%) participants referred their oral and maxillofacial region cases to OMS. Almost 50% of the participants had come across a patient of facial trauma, and 50% had not encountered a patient with such trauma. Most of the medical practitioners (62.4%) were aware of the fact of cosmetic and orthognathic surgery as becoming a routine procedure in the field of oral and maxillofacial surgery. Regarding the evolution of the surgical skills from the simple closure of wounds to the microvascular reconstruction of various jaw defects, most of the medical practitioners were agreeing (95.76%). Sixty - seven participants had shown positivity towards the inclusion of the oral and maxillofacial surgeon in the panel of experts. Sixty -nine medical practitioners felt the term “oral and maxillofacial surgery” is winded and complicated (Table 1, Fig.1).

Table 1: Responses of the medical practitioners to the different questionnaire for the speciality of the oral and maxillofacial surgery

Are you aware of oral maxillofacial surgery as a speciality branch of dentistry?	105 (84%)	20 (16%)
Are you aware of the different variety of treatment modalities coming under oral and maxillofacial surgery?	52 (41.6%)	73 (58.4%)
Have you referred oral and maxillofacial region cases to an oral surgeon?	50 (40%)	75 (60%)
Have you ever come across a patient with facial trauma?	62 (49.6%)	63 (50.4%)
Are you aware of the fact that Cosmetic and orthognathic surgery is becoming a routine procedure in the field of oral and maxillofacial surgery?	78 (62.4%)	47 (37.6%)
Will you agree that Oral and maxillofacial surgeons have improvised their surgical skill and competence from simple closure of the wounds to microvascular reconstruction of various jaw defects?	95 (76%)	30 (24%)
Would you like to include oral and maxillofacial surgeon in your panel expertise for delivery of treatment?	67 (53.6%)	58 (46.4%)
Is the name of the speciality “oral and maxillofacial surgery” is winded and complicated?	56 (44.8%)	69 (55.2%)

Medical practitioners were also asked about the management of various conditions. Most of the medical practitioners knew that Wisdom tooth removal is in the scope of the oral and maxillofacial surgeon. But in case of cleft lip and palate, most of the medical practitioners (65) agreed that it is managed by the plastic surgeon, and only forty - five believed the OMS manages it.

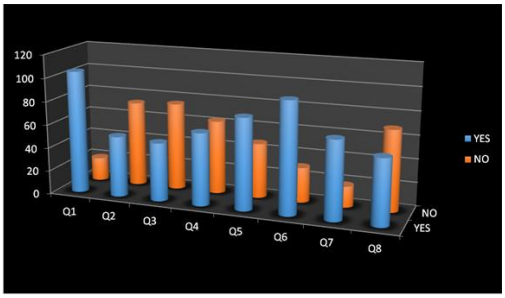

Figure 1: Responses of the medical practitioners to the different questionnaire for the speciality of the oral and maxillofacial surgery

Oral cancer management according to 80 participants was by the OMS, while 29 participants thought it is managed by the general surgeon and 17 by the ENT surgeon. For facial swellings, most of the practitioners (50) believe that it should be managed by the general surgeon. Facial space infections and dental implants were the two procedures, which medical practitioners (76 and 91, respectively) agreed it is a speciality procedure of OMS. While participants’ answers ranged randomly among different specialities regarding the management of trigeminal neuralgia, facial injuries, jaw pathologies and lumps in the

mouth. For the facial fractures, 76 medical practitioners believe that it is within the scope of orthopaedic surgery.

Table 2: Responses of the medical practitioners for the management of the various conditions

Patient's complaint	ENT surgeon	Plastic surgeon	The oral and maxillofacial surgeon	General surgeon	Orthopaedic surgeon
Wisdom tooth removal	1	2	114	6	2
Cleft lip and palate	10	65	45	8	5
Oral cancer	17	7	80	29	2
Facial neck swelling	39	5	34	50	3
Facial space infections	34	10	76	7	0
Dental implants	10	15	91	5	5
Trigeminal neuralgia	25	10	57	30	6
Facial cut injuries	2	38	43	38	3
Jaw pathologies	12	5	67	28	13
A lump in the mouth	5	1	60	58	3
Facial bone fractures	6	4	40	4	76
Facial abscess	3	7	36	81	0
Sinus problems	75	12	20	17	1
Aesthetic surgery	7	72	38	7	2
TMJ disorders	51	20	55	2	2
Jaw deformities	3	4	80	8	31

Similarly, for the facial abscess and sinus problems, 81 and 75 practitioners thought it is the job of the general surgeon and ENT surgeon respectively. While for aesthetic surgery, 72 participants had shown positivity for the plastic surgeon and only 38 for the oral surgeon. (Table 2, Fig 2a, b, c, and d).

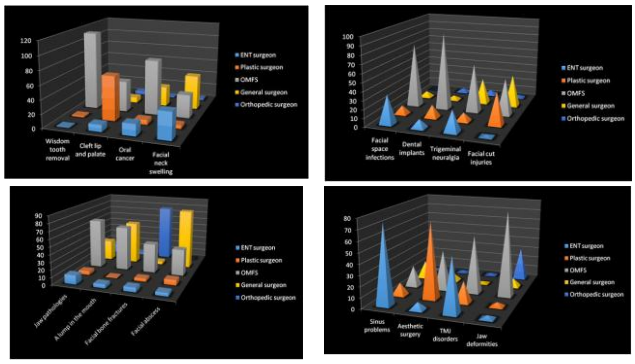

Figure 2: a) Responses of the medical practitioners for the management of the various conditions; b) Responses of the medical practitioners for the management of the various conditions; c) Responses of the medical practitioners for the management of the various conditions; d) Responses of the medical practitioners for the management of the various conditions

Discussion

When the name of the field of "oral surgery" was altered to "oral and maxillofacial surgery" in 1977, the goal was to more clearly define the scope of practice of the field to the public. Since then, there has been a significant argument, whether this objective has been accomplished. In trying to answer this question, it is important to study the knowledge and awareness of the medical practitioners [4].

OMFS includes treatment of many diseases, defects and injuries in the head, face, neck, jaws and also the hard and soft tissues of the oral and maxillofacial region. OMFS is an internationally accepted surgical speciality. In some countries, like in the United States, it is an accepted speciality of dentistry; while in others, such as in the UK, it is a speciality that requires a degree in medicine [1]. In Saudi Arabia, the OMFS is recognised as a speciality branch of dentistry.

The scope of the OMFS improved from simple surgical procedures such as dentoalveolar surgeries and basic maxillofacial trauma to more advanced procedures like management of pathologies of head and neck (both benign and malignant), bone grafting, craniofacial surgery, TMJ surgery, cleft lip and palate, facial deformities correction, aesthetic facial surgery, implant surgery, etc [1] [5]. Also, OMFS deals with non - surgical difficulties affecting the orofacial area like the treatment of facial pain or oral mucosal disease [1] [6].

Patients usually reach to their general medical practitioners, emergency departments or dentists with pathologies or abnormalities requiring referral to an oral and maxillofacial surgeon [4].

Basic knowledge of the speciality should be given to our medical colleagues for the benefit of the patients in making informed decisions. Also, the general public can benefit from knowing OMFS scope so that they can request appropriate referrals [3] [7].

In the present study, the knowledge and awareness of the medical practitioners about the oral and maxillofacial surgery were found to be low. Also, the scope of the management of the various conditions was found not to be in favour of the oral and maxillofacial surgeons and most of the conditions shown management by another medical speciality.

Ameerally et al., [8] done a study in England and shown that around 74% did not understand OMS role and scope and up to 79% of the general population had not heard of OMFS. Similarly, Ifeacho et al. [7] shown that most of the medical practitioners who had heard of OMFS, selected other specialities for management of conditions that might have some overlap with other disciplines. Hunter et al. [9] concluded in their study that medical persons who know about OMFS, their design for management of various conditions overlapping various specialities did not select oral and maxillofacial surgery.

As one of the nine surgical disciplines recognised internationally, OMFS is also recognised by the Saudi Health minister and the Saudi Commission for health specialities. The need for the

services of OMS in Saudi Arabia is ever increasing especially with the very high prevalence of road traffic accidents and also the high incidence of oral cancers, particularly in the southern regions.

There is the Saudi Society for Oral and Maxillofacial Surgery (SCOMS) which has an important role in providing advice to the government bodies to set regulations and guidelines for the practice of OMFS in the country. It also plays a major role in the promotion of the speciality among the general public and the health providing communities. The SCOMS recognises the low awareness toward the speciality in both the general and medical communities.

In conclusion, there is low awareness about the scope of oral and maxillofacial surgery among the medical practitioners. Knowledge and awareness of the scope of oral and maxillofacial surgery can improve the success and the delivery of quality service. Also, there is a need to increase the awareness of OMFS among the general public so that they can request their doctors for the appropriate referral pattern in Saudi Arabian cities.

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