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Basic Science

HLA Genotyping in Patients with End-Stage Renal Disease Waiting For Cadaveric Renal Transplantation in Federation of Bosnia and Herzegovina

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Abstract

AIM: The research was conducted by genotyping two Human Leukocyte Antigen (HLA) gene classes. The main objective of this research was to investigate distribution and frequency of the allelic groups, genotypes and haplotypes in the gene loci of HLA class I (HLA-A*, -B*, -C*) and HLA class II (HLA-DRB1*, -DQB1*) in patients included in the program of cadaveric renal transplantation.

MATERIAL AND METHODS: Our study covered 186 blood samples of patients who are registered on the list for cadaveric renal transplantation in Federation of Bosnia and Herzegovina and included 59 control, healthy unrelated individuals. For the HLA typing, we have used three different methods: micro lymphocyte cytotoxicity test (MLCT), Polymerase Chain Reaction (PCR) – Sequence Specific Primers (SSP) and PCR – Sequence-Specific Oligonucleotides (SSO) or Luminex technology. All patients and cadaveric donors were tested using the three methods because the system is polymorphic.

RESULTS: Analysis of the results of genotyping HLA class I gene loci identified dominant HLA-A*02, HLA-B*35, HLA-C*07 allelic groups. Analysis of the HLA class II gene loci genotyping showed that HLA-DRB1*11 and HLA-DQB1*03 loci had the highest incidence in HLA class II.

CONCLUSION: Based on our results and previous research, there were no observed differences between allelic frequencies and genotypes of healthy people and people with ESRD. Differences between allelic groups occurred, but they were not statistically significant, except HLA-C*01 ($p = 0.020$).

Introduction

The main problem with renal transplantation is the lack of suitable dead donors. The improvements in molecular genotyping methods, diagnostics and therapy for maintaining transplants, upgrade the transplantation process, however, the number of dead donors is not increasing, while transplantation lists and the need for dead transplants continues to grow each year [1]. Kidney transplants from live donors produce better results, including faster rehabilitation and better success rate. Another advantage is the increase in the number of available organs. Higher tissue HLA matching between donors and recipients contributes to the longer survival of transplanted organs [2]. Many transplant centres are limited to living organ donors only. When the donors are divided into groups by degree of HLA compatibility with the organ recipient, a better result in the survival of transplant has been achieved in the cases of higher HLA compatibility. This fact is especially true when the unrelated persons (or distant relatives) are kidney donors [3, 4]. Living organ transplantation should be considered for each organ recipient. MHC antigens, which have proven to be important in kidney

transplantation, are HLA-A, HLA-B and HLA-DR markers. As these antigens were determined by the genes of both parents, at least six antigens of the recipient (2A, 2B and 2DR) must correspond with the antigens of the potential donor [5]. If the kidney has been taken from a family member, parents or siblings, it is necessary that there is a correspondence in three loci, and partial coincidence in less important, but other present genes HLA-C, HLA-DP and HLA-DQ [6]. Value of the haplotype synchronizing (0, 1, 2) was determined clinically: siblings with two identical haplotypes can expect survival of 90% of transplants after one year, parents and siblings with the same haplotype after one year achieved graft survival of 75%, and members of the same family without equal haplotypes achieve survival of 50% of the grafts after one year [7]. The main problem in transplantation is the immune response of T and B lymphocytes of the host [8]. The most preferred method for the prevention of transplant rejection is achieving sufficient antigen matching between donor and recipient, as with identical twins. Good acceptance of the transplanted tissue or organ is already achieved if the donor and recipient are matched in MHC-II class of antigens (in particular HLA-DR) since they directly activate T-helper lymphocytes of the recipient [9, 10]. HLA antigens are the main target of immune response which leads to the rejection of transplanted organs. For the purpose of transplantation, a state of the histocompatibility between donor and recipient exists only when the immune response is absent or controlled to foreign graft survive [11]. The reaction of transplant rejection is an immune response, directed primarily towards the molecules of the main histocompatibility system or MHC antigens and other mismatched graft antigens [12, 13].

The main objective of this research was analysis of distribution and frequency of the allelic groups, genotypes and different haplotypes in the gene loci of HLA class I (HLA-A*, -B, -C*) and HLA class II (HLA-DRB1*, -DQB1*) in patients who have been included in the program of cadaveric renal transplantation in Federation of Bosnia and Herzegovina (FB&H) for period 2007-2012.

Materials and Methods

The sample included 186 patients. All patients were in End Stage Renal Disease (ESRD) who were included in the program of cadaveric kidney transplantation in FB&H, and they are not related by blood kinship relations. Research covered patients from 9 hemodialysis center: Sarajevo (39 male; 16 women), Zenica (29 male; 12 women), Bihać (13 male; 11 women), Tešanj (13 male; 10 women); Travnik (8 male; 5 women), Mostar +Konjic (4 male; 4 women), Živinice + Gračanica (8 male; 1 women), Odžak (6 male; 2 women). Mean age was 49 ± 7 years. Our research on patients was undertaken in compliance with all applicable guidelines, which aim to ensure the proper implementation of the safety of persons participating in the scientific research, including Fundamentals of Good Clinical Practice, Declaration of Helsinki 1975, as revised in 2008, and in the accordance with the approval of the Ethics Committee of the Institute (Approval No. 01-3-3558 23.6.2016). Genotyping included 59 healthy individuals that are not related to the patients; they represented control group.

HLA genotyping

Samples of venous blood were taken into vacutainer tubes with anticoagulant heparin (serological analysis), and samples of venous blood were taken into vacutainer tubes with anticoagulant EDTA (ethylene diamine tetra acetyl acid – molecular analysis). Isolation of DNA was carried out using the kit for DNA, Ready – DNA Spin Kit (Inno-train, Germany). The HLA genotyping was performed by using three different methods: 1) phenotyping of HLA class I (A, B and C) was done by using micro lymphocyte cytotoxicity test (MLCT); 2) genotyping of HLA class I (HLA-A*, -B* and -C*) and HLA class II (HLA-DRB1* and -DQB1*) was performed by low resolution or by using the Polymerase Chain Reaction (PCR) qualitative detection of sequential specific PCR products by agarose gel electrophoresis (method is based on the PCR-SSP or Sequence Specific Primers); 3) genotyping of HLA class I (HLA-A*, -B* and -C*) and HLA class II (HLA-DRB1* and -DQB1*) was also performed by low resolution, using asymmetric PCR with different primers for each sample. After amplification of the PCR products labelled with biotin, they were mixed and bind to complementary probes during hybridization process (method based on PCR-SSO or Sequence-Specific Oligonucleotides). This technology is also called Luminex technology or technology of fluoroanalyser with microspheres.

Statistical analysis

The frequency of genotypes, gene variants was estimated according to estimation-maximization (EM) algorithm which has been implemented in a computer software PowerMarker v3.25 (Bioinformatic program, Raleigh, NC, USA) and OpenEpi v3.01. [14]. Software for calculating risk ratios (OR) using 2x2 contingency tables was also used. To calculate the statistical significance of the differences in the frequencies of gene variants, and genotypes of the control group and the patients, the Fisher accuracy test, with $P > 0.05$ was used.

Results

The frequencies of allelic groups of HLA class I (HLA-A*, -B*, -C*) are shown in Table 1. The highest frequency of the allelic groups of HLA-A* gene locus had HLA-A*02 (0.2930) in patients and control group HLA-A* (0.2797). The lowest frequency allelic groups were HLA-A*30 and A*31, while they weren't recorded in the control group.

Table 1: Frequency of allelic groups HLA-A*, HLA-B* and HLA-C* between control and experimental group

a) HLA-A* allelic groups

n	Patients	2n	Frequency fa	Control	2n	Frequency fa	p-values
1.	A*01	68	0.1828	A*01	17	0.1441	0.277
2.	A*02	109	0.29301	A*02	33	0.2797	0.717
3.	A*03	39	0.10484	A*03	10	0.0847	0.503
4.	A*11	23	0.06183	A*11	12	0.1017	0.127
5.	A*24	36	0.09677	A*24	13	0.1102	0.654
6.	A*25	13	0.03495	A*25	4	0.0339	0.956
7.	A*26	26	0.06989	A*26	9	0.0763	0.807
8.	A*30	9	0.02419	A*30	/	-	-
9.	A*31	9	0.02419	A*31	/	-	-
10.	A*32	12	0.03226	A*32	4	0.0339	0.929

b) HLA-B* allelic groups

n	Patients	2n	Frequency fa	Control	2n	Frequency fa	p-values
1.	B*07	21	0.05645	B*07	4	0.0339	0.318
2.	B*08	34	0.0914	B*08	8	0.0678	0.401
3.	B*13	15	0.04032	B*13	2	0.0169	0.218
4.	B*18	27	0.07258	B*18	11	0.0932	0.445
5.	B*27	15	0.04032	B*27	5	0.0424	0.920
6.	B*35	45	0.12097	B*35	17	0.1441	0.477
7.	B*38	17	0.0457	B*38	4	0.0339	0.572
8.	B*44	42	0.1129	B*44	8	0.0678	0.134
9.	B*51	54	0.14516	B*51	15	0.1271	0.591
10.	B*57	17	0.0457	B*57	5	0.0424	0.820

c) HLA-C* allelic groups

n	Patients	2n	Frequency fa	Control	2n	Frequency fa	p-values
1.	C*01	41	0.11022	C*01	5	0.0424	0.020*
2.	C*02	38	0.10215	C*02	8	0.0678	0.239
3.	C*03	21	0.05645	C*03	8	0.0678	0.638
4.	C*04	66	0.17742	C*04	22	0.1864	0.813
5.	C*05	20	0.05376	C*05	4	0.0339	0.371
6.	C*06	41	0.11022	C*06	12	0.1017	0.781
7.	C*07	120	0.32258	C*07	36	0.3051	0.626
8.	C*08	5	0.01344	C*08	1	0.0085	0.667
9.	C*12	9	0.02419	C*12	15	0.1271	<0.001*
10.	C*14	3	0.00806	C*14	2	0.0169	0.400

*, Statistically different in comparison with control.

Among allelic groups of HLA-B* gene locus the most usual allelic groups were HLA-B*51 (0.1451) in patients group and HLA-B*35 (0.1209) in control group, while allelic groups HLA-B*13 and B*27 in patients group and allelic groups HLA-B*13 in control group had the lowest frequency.

The highest frequency of HLA-C* gene locus had following allelic group HLA-C*04 (0.1774) in patients group and HLA-C*07 (0.3051) at healthy, control group while the lowest frequency value had allelic group C*14 in patients group and C*08 in control group. Significant differences between both groups were recorded for HLA-C*01 and C*12 allelic groups.

Genotyping of HLA class II gene loci determined presence HLA-DRB1*11 allele group with highest frequencies of patients group and HLA-DRB1*13 in control group. Results of analysis of DRB1* gene locus are shown in Table 2.

The highest frequency within the HLA-DQB1* gene locus had allelic group DQB1*03 (0.3333), and HLA-DQB1* 06 is very frequently in both group. It was not noticed an absence of any allelic group in HLA-DQB1* gene locus. Results of analysis of DQB1* allelic groups are shown in Table 2.

Table 2: Frequency of HLA-DRB1* and HLA-DQB1* gene loci between control and experimental group

HLA-DRB1*

n	Patients	2n	Frequency fa	Control	2n	Frequency fa	p-values
1.	DRB1*01	45	0.12097	DRB1*01	13	0.1102	0.733
2.	DRB1*03(17)	43	0.11559	DRB1*03(17)	16	0.1356	0.531
3.	DRB1*04	47	0.12634	DRB1*04	9	0.0763	0.110
4.	DRB1*07	29	0.07796	DRB1*07	9	0.0763	0.950
5.	DRB1*08	14	0.03763	DRB1*08	5	0.0424	0.812
6.	DRB1*11	57	0.15323	DRB1*11	15	0.1271	0.443
7.	DRB1*13	38	0.10215	DRB1*13	20	0.1695	0.030*
8.	DRB1*14	22	0.05914	DRB1*14	5	0.0424	0.751
9.	DRB1*15	36	0.09677	DRB1*15	13	0.1102	0.654
10.	DRB1*16	29	0.07796	DRB1*16	11	0.0932	0.580

HLA-DQB1*

n	Patients	2n	Frequency fa	Control	2n	Frequency fa	p-values
1.	DQB1*02	68	0.1828	DQB1*02	22	0.1864	0.919
2.	DQB1*03	124	0.48334	DQB1*03	36	0.3050	0.427
3.	DQB1*04	12	0.03226	DQB1*04	3	0.0254	0.702
4.	DQB1*05	106	0.28495	DQB1*05	28	0.2373	0.200
5.	DQB1*06	62	0.16667	DQB1*06	29	0.2458	0.028*

*, Statistically different in comparison with control.

HLA-A* gene locus analysis revealed 63 different HLA-A* genotypes for 186 observed patients (Table 3.). The most common genotypes were HLA-A*02/A*02 (0.1022), and HLA-A*01/A*02 (0.0753).

Table 3: Frequency of HLA-A* genotypes between control and experimental group

HLA-A* genotypes

n	Patients	n	Genotype frequency	Control	n	Genotype frequency	p-values
1.	A*01/A*01	7	0.0376	A*01/A*01	/	/	-
2.	A*01/A*02	14	0.0753	A*01/A*02	5	0.0847	0.812
3.	A*01/A*03	11	0.0591	A*01/A*03	/	/	-
4.	A*01/A*24	8	0.043	A*01/A*24	3	0.0508	0.800
5.	A*01/A*26	6	0.0323	A*01/A*26	1	0.0169	0.460
6.	A*02/A*02	19	0.1022	A*02/A*02	4	0.0678	0.424
7.	A*02/A*03	14	0.0753	A*02/A*03	4	0.0678	0.848
8.	A*02/A*11	8	0.043	A*02/A*11	5	0.0847	0.107
9.	A*02/A*24	11	0.0591	A*02/A*24	4	0.0678	0.809
10.	A*02/A*26	7	0.0376	A*02/A*26	3	0.0508	0.654

Within the HLA-B* gene locus, in 186 patients, an analysis revealed 96 different genotypes (Table 4). The most common genotypes were HLA-B*35/B*44 (0.0484) and HLA-B*08/51*B (0.0376). In the control group, the most frequent genotypes in B* locus are HLA-B*08/51 and HLA-B*35/51 (0.0508).

Table 4: Frequency of HLA-B* genotypes between control and experimental group

HLA-B* genotypes

n	Patients	n	Genotype frequency	Control	n	Genotype frequency	p-values
1.	B*07/B*35	5	0.0269	B*07/B*35	1	0.0169	0.667
2.	B*07/B*44	4	0.0215	B*07/B*44	/	/	-
3.	B*08/B*44	6	0.0323	B*08/B*44	/	/	-
4.	B*08/B*51	7	0.0376	B*08/B*51	3	0.0508	0.654
5.	B*13/B*18	6	0.0323	B*13/B*18	1	0.0169	0.538
6.	B*18/B*51	4	0.0215	B*18/B*51	1	0.0169	0.829
7.	B*35/B*35	5	0.0269	B*35/B*35	1	0.0169	0.667
8.	B*35/B*44	9	0.0484	B*35/B*44	2	0.0339	0.639
9.	B*35/B*51	5	0.0269	B*35/B*51	3	0.0508	0.366
10.	B*38/B*44	4	0.0215	B*38/B*44	/	/	-
11.	B*38/B*51	4	0.0215	B*38/B*51	1	0.0169	0.829
12.	B*39/B*51	4	0.0215	B*39/B*51	1	0.0169	0.829
13.	B*51/B*51	6	0.0323	B*51/B*51	/	/	-

Within the HLA-C* gene locus it was found 37 different genotypes (Table 5), the most common genotypes were HLA-C*07/07*C (0.1774), HLA-C*04/04*C (0.1022) and HLA-C*04/07*C (0.0699) in patients group. In the control group, the most frequent genotype is HLA-C*07/07*C (0.1356).

Table 5: Frequency of HLA-C* genotypes between control and experimental group

HLA-C* genotypes							
n	Patients	n	Genotype frequency	Control	n	Genotype frequency	p-values
1.	C*01/ C*01	10	0.0538	C*01/ C*01	/	/	-
2.	C*02/ C*02	7	0.0376	C*02/ C*02	/	/	-
3.	C*02/ C*07	7	0.0376	C*02/ C*07	1	0.0169	0.436
4.	C*03/ C*07	7	0.0376	C*03/ C*07	1	0.0169	0.436
5.	C*04/ C*04	19	0.1022	C*04/ C*04	3	0.0508	0.230
6.	C*04/ C*07	13	0.0699	C*04/ C*07	5	0.0847	0.703
7.	C*07/ C*07	33	0.1774	C*07/ C*07	8	0.1356	0.453
8.	C*01/ C*06	7	0.0376	C*01/ C*06	/	/	-
9.	C*06/ C*06	7	0.0376	C*06/ C*06	/	/	-
10.	C*06/ C*07	12	0.0645	C*06/ C*07	5	0.0847	0.086

Within the HLA-DRB1* gene locus it was determined the presence of 58 different genotypes, including the most common HLA-DRB1*01/DRB1*11 (0.0430), HLA-DRB1*04/DRB1*11 and HLA-DRB1*13/DRB1*16 genotype (0.0376) in patients group.

Table 6: Frequency of HLA-DRB1* genotypes between control and experimental group

HLA-DRB1* genotypes							
n	Patients	n	Genotype frequency	Control	n	Genotype Frequency	p-values
1.	DRB1*01/ DRB1*11	8	0.043	DRB1*01/ DRB1*11	/	/	-
2.	DRB1*01/ DRB1*04	6	0.0323	DRB1*01/ DRB1*04	1	0.0169	0.538
3.	DRB1*03(17)/ DRB1*11	6	0.0323	DRB1*03(17)/ DRB1*11	1	0.0169	0.538
4.	DRB1*03(17)/ DRB1*16	6	0.0323	DRB1*03(17)/ DRB1*16	2	0.0339	0.950
5.	DRB1*04/DRB1*07	6	0.0323	DRB1*04/DRB1*07	3	0.0508	0.508
6.	DRB1*04/ DRB1*11	7	0.0376	DRB1*04/ DRB1*11	2	0.0339	0.894
7.	DRB1*11/ DRB1*14	6	0.0323	DRB1*11/ DRB1*14	3	0.0508	0.508
8.	DRB1*11/ DRB1*15	6	0.0323	DRB1*11/ DRB1*15	1	0.0169	0.538
9.	DRB1*13/ DRB1*16	7	0.0376	DRB1*13/ DRB1*16	/	/	-

Research results within the HLA-DQB1* gene locus revealed 27 different genotypes. The most usual genotypes were HLA-DQB1*03/DQB1*05 (0.2204) and HLA-DQB1*02/DQB1*03 (0.1667) in patients group. The genotype HLA-DQB1*02/DQB1*03 is the most frequent in the control group.

Table 7: Frequency of HLA-DQB1* genotypes between control and experimental group

HLA-DQB1* genotypes							
n	Patients	n	Genotype frequency	Control	n	Genotype frequency	p-values
1.	DQB1*02/ DQB1*02	8	0.043	DQB1*02/ DQB1*02	/	/	-
2.	DQB1*02/ DQB1*03	31	0.1667	DQB1*02/ DQB1*03	10	0.1694	0.959
3.	DQB1*02/ DQB1*05	21	0.1129	DQB1*02/ DQB1*05	4	0.0678	0.318
4.	DQB1*03/ DQB1*03	21	0.1129	DQB1*03/ DQB1*03	3	0.0508	0.162
5.	DQB1*03/ DQB1*05	41	0.2204	DQB1*03/ DQB1*05	7	0.1186	0.086
6.	DQB1*03/ DQB1*06	22	0.1182	DQB1*03/ DQB1*06	8	0.1356	0.723
7.	DQB1*05/ DQB1*05	13	0.0699	DQB1*05/ DQB1*05	6	0.1017	0.426
8.	DQB1*05/ DQB1*06	14	0.0753	DQB1*05/ DQB1*06	3	0.0508	0.520

Discussion

HLA class I molecules can be found on the surface of all cells that contain the nucleus, while class II of HLA molecules can be constitutively found on the surface of certain types of cells (dendritic cells, macrophages, B-lymphocytes. HLA-DR (not HLA-DQ, -DP, or -DM) is abundantly expressed on the endothelial cells of peritubular and glomerular capillaries [15].

Table 8: Frequency of allelic group with Odds Ratio (OR) and p-values between control and patients group

		Patients		Control		
Allelic groups	2n	Allele frequency	2n	Allele frequency	OR	p-values
HLA-C*01	41	0.11022	5	0.0424	2.799	0.020
HLA-C*12	9	0.02419	15	0.1271	0.1702	0.0000063
HLA-DRB1*13	38	0.10215	20	0.1695	0.5575	0.030
HLA-DQB1*06	62	0.16667	29	0.2458	0.6138	0.0280

The explanation for the improved survival of kidney allografts in which HLA have good congruence was: lower occurrence of anti-HLA antibodies [16], lower occurrence of alloreactive CD4+ T-cells or absence of direct CD4+ T-cell response to HLA-DR matched graft [17], fewer peptide epitopes stimulate response of T-helper cells of "indirect way" which includes chronic rejection of allograft [18]. HLA matching in HLA-A, HLA-B and HLA-DR loci increases the likelihood of developing a donor antigen-specific regulatory T-cells [19].

Benefits of HLA matching has an impact on different outcomes in terms of number of days spent in hospital, failure of graft function [20, 21], episodes of rejection, the one-year and three-year levels of serum creatinine [22], on prediction of long-term outcome of the disease, on status of patients and on multivariate analysis [23, 24].

Chronic renal failure (CRF) leads in most cases to ESRD, with final result – kidney transplantation process. There is an interest to assess connection of class I and II of HLA antigens with ESRD or CRF renal diseases [25].

In hemodialysis patients that are the part of cadaveric renal transplantation program in FB&H it was observed that the HLA antigens with the greatest frequency were: HLA-A*02 = 0.29301, HLA-B*51 = 0.14516, HLA-C*07 = 0.32258, HLA-DRB1*11 = 0.15323 and HLA-DQB1*03 = 0.48334. The antigens that showed in control group greatest frequency were: HLA-A*02= 0.2797, HLA-B*35= 0.1441, HLA-C* = 0.03051, HLA-DRB1*13 = 0.1695 and HLA-DQB1*03 = 0.3050. In the analysis of allelic groups in each locus, with estimation of the p-value, the allelic group HLA-A* showed no statistically significant difference in the aforementioned allelic groups. Such results were also recorded when comparing the frequencies of allelic groups in HLA-B*. Locus C* showed a statistically significant difference in the frequency of the allelic HLA-C*01 with p = 0.020 and OR = 2.601,

that is considered as an allelic group of high risk, and it showed a difference in the allelic HLA-C*12 with p = 0.0000679. Although the OR value is 0.190, this allelic group can't be considered protective. The HLA-DRB1* locus also showed statistical significance in frequencies in the allelic HLA-DRB1*13 (p = 0.030) with OR = 0.6027, and it is not at risk of developing ESRD. The allelic group HLA- DQB1*06 showed statistical significance (p = 0.028) and OR = 0.6138, and it is not considered as a group of high risk, as shown in Table 3.

Our research covered hemodialysis patients included in program of cadaveric renal transplantation in FB&H. The HLA class I (HLA-A*, -B*, -C*) genotypes with the highest incidence were: A*02/A*02 = 0.1022, B*35/B*44 = 0.0484, C*07/07 = 0.1774. HLA class II genotypes with highest incidence were: DRB1*01/DRB1*11 = 0.043 and DQB1*03/DQB1*05 = 0.2204.

Based on our results and previous research, there were no observed differences between allelic frequencies and genotypes of healthy people and people with ESRD. Differences between allelic groups occurred, but they were not statistically significant, except HLA-C*01, p = 0.020.

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Sensitivity to Antimicrobial Drugs of *Pseudomonas Aeruginosa* Extreme-Resistant Strains Isolated in the Major Hospitals of Central Kazakhstan

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Keywords: *Pseudomonas aeruginosa*; carbapenemases gene; Antibiotic resistance; MALDI-TOF; VIM.

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Abstract

AIM: The article presents the current data on the sensitivity of the main 37 strains of eXtremaly Drugs Resistance (XDR) category to anti-pseudomonas drugs.

MATERIAL AND METHODS: The strains were collected during the prospective multicenter study in large multidisciplinary hospitals of Central Kazakhstan. Susceptibility to antimicrobial drugs was carried out by disk method and the serial dilution method with the interpretation of the results according to EUCAST criteria. Detection of carbapenemases gene of VIM, IMP, NDM and GES classes was carried out by PCR method using the commercial kits.

RESULTS: All identified carbapenemases were sorted to VIM class and accounted for 63.64%. Resistance to aminoglycoside drugs exceeded 80%. All the strains were susceptible to polymyxin.

CONCLUSION: Thus, at the present stage the circulation of P. aeruginosa strains of XDR category continues in major hospitals in Kazakhstan. The strains remain sensitiveness only to polymyxin.

Introduction

Antibiotic resistance as a phenomenon of microorganisms' insensibility to achievable concentrations of antibiotics in clinical conditions has become in the last 20 years the pattern of the global problem, migrated from the level of individual departments and hospitals to the level of a global epidemic process, threatening the future of humanity.

Every year more than 20 thousand patients die in the USA in the result of infectious processes caused by multidrug-resistant microorganisms. The USA government spends more than 20 billion dollars a year for the control of antibiotic-resistant strains spreading [1].

The EU countries annually spend more than 9 billion euros for the solution of the problem. At the same time in the European Union more than 25 thousand patients a year die because of ineffective antimicrobial chemotherapy, and more than half of the cases caused by Gram-negative microorganisms [2]. The last in most cases have multidrug resistance mechanisms, leading to a significant narrowing of the list of choice drugs and in the cases of pan-resistance – to almost no alternative solutions [3].

Till recently carbapenems were regarded as the drugs of extreme selection. However wide spreading of carbapenemases genes significantly expanded the list of problematic strains in which of *Pseudomonas aeruginosa* is regarded as a classic representative [4]. Modern strains of *P. aeruginosa* in addition to many natural mechanisms and

antimicrobial resistance mechanisms due to the high genetic lability constantly replenish its arsenal of acquired resistance mechanisms [5] and have the predilection to the clonal global spreading [6]. From this perspective, the continuous supervision for the local spread of multidrug-resistant strains is important for practical health care as well as for fundamental science. The strains of XDR (eXtremaly Drugs Resistance) category [7] are the particular problem for medicine because of extreme multi-resistance to a wide range of antimicrobial agents.

Our study focuses on the description of the sensitivity of antimicrobial agents and detection of genes that determine resistance to carbapenems in of *P. aeruginosa* strains of XDR category, isolated in large hospitals of Central Kazakhstan.

Materials and Methods

The study included strains collected in the period from 2015 to 2016 during the prospective multicenter microbiological research covering large multidisciplinary hospitals of Central Kazakhstan (Karaganda and Astana).

Isolation of strains was conducted in local bacteriological laboratories of participating centres, and after the strains were forwarded to the microbiology laboratory of the Scientific-Research Center of Karaganda State Medical University, where it was conducted the re-identification methods of time-of-flight mass-spectrometry (MALDI-TOF) using MALDI-Biotyper software (Bruker). Determination of sensitivity to antimicrobial agents was conducted by disk- diffusion method and by the method of serial microdilution in a liquid medium according to EUCAST recommendations [8].

The primary test for detection of Metallo-beta-lactamase activity was carried out with 100 mM EDTA by the recommendations [9]. Additional screening CIM test for detection of carbapenemases activity was carried out by the recommendations [10].

The presence of carbapenemases genes of VIM and IMP classes were performed by Real-Time PCR methods using the commercial kit «AmpliSens MDR MBL-FL» produced by Interlab Service (Russia).

Statistical processing was performed by determining the average values, the definition of rank correlation coefficient by Spearman and determining the 95% confidence interval for the mean values by Klopper-Pearson with the use of MS Excel and Whonet 6.5 [11].

Results

As a result of screening, it was selected 37 strains with XDR phenotypic profile among 270 strains collected in large multidisciplinary hospitals of Central Kazakhstan.

Data on antimicrobial resistance is shown in Figure 1.

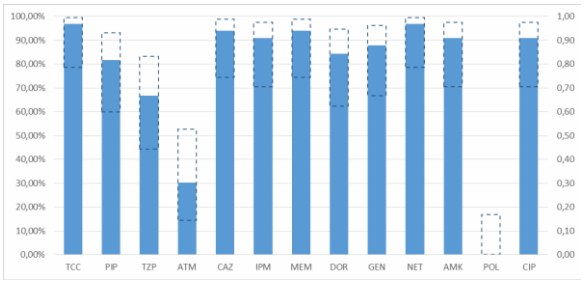

Figure 1: The share of non-sensitive (%R+%I) hospital P. aeruginosa strains to antimicrobial drugs. The dotted squares represent 95% confidence intervals

The studied strains were characterised by resistance to the absolute majority of drugs with anti-pseudomonas activity. The exception was polymyxin, to which we did not reveal any resistant strain. Taking into account the trend towards the emergence of resistant strains of *P. aeruginosa* to colistin [12] we carried out a quantitative evaluation of the sensitivity of the studied strains to polymyxin.

MIC50 for studied strains was 0.5 μg/ml but MIC range was 0.5-2 μg/ml. This pattern suggests polymyxin as the only available anti-pseudomonas drug with high activity, and it actualizes the questions on the development of technologies increasing the bioavailability of the drug [13]. Sensitivity to aztreonam was observed in more than half of the cases (51.43%; 95% CI, 31.25-71.15). A similar pattern is due to the high frequency of occurrence of strains producing Metallo-beta-lactamase (B class) hydrolyzing all beta-lactams except aztreonam [14], which proportion was 68.75%.

Genetic typing of the mechanisms of resistance to carbapenems identified the carbapenemases genes of VIM class, the proportion of strains producing carbapenemases of VIM class was 63.64% (95% CI 39.63-81.17). Meanwhile, the test with chelating agent EDTA showed inhibitory activity in 31 strains that in combination with MIC values corresponding to the expected moderate stability permit to expect the low-affinity carbapenemases of GES class. However, conducted research has not revealed GES carbapenemases genes. Ecoff analysis of distributions on imipenem (Fig. 2) allows surmising sampling heterogeneity.

According to that 75% isolates have MIC higher 32 μg/ml we expected an equal number of

producers of carbapenemases. At the same time, PCR detection of VIM producers was positive in 63.64% which is clearly linked to other mechanisms of resistance. Strains with moderate resistance imipenem were moderately resistant to meropenem and also to aminoglycosides that can be connected with other on- enzymatic resistance mechanisms [15].

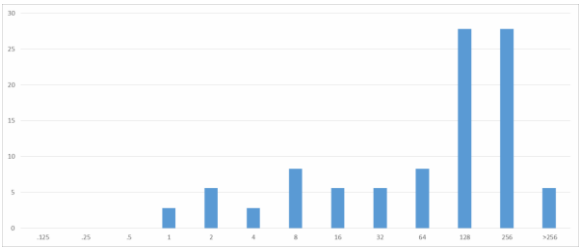

Figure 2: Ecoff distribution of MIC imipenem for studied P. aeruginosa strains (boundary values 4-16 µg/ml), S – sensitive population, I – moderately resistant, R – resistant population

Resistance to fluorinated quinolones was detected in more than 90%, the average MIC values were extremely high too (>32 µg/ml). Resistance to ciprofloxacin had a strong positive correlation with resistance to levofloxacin, which is obviously connected with the general resistance mechanisms and can approximate these results to the whole group of fluorinated quinolones.

Discussion

At present the only drug with a high-clinically significant activity against studied pan-resistant *P. aeruginosa* strains is polymyxin. We did not reveal any cases of resistance; all the studied strains had MIC less than 1 µg/ml. The average values of the MIC of polymyxin totalled 0.49 µg/ml.

The resulting picture clearly shows that there is no alternative situation on the choice of drugs for the causal treatment of infections caused by extremely resistant *P. aeruginosa* strains.

Thus, at the present stage, the circulation of *P. aeruginosa* strains of XDR category continues in major hospitals in Kazakhstan, which have been shown previously [16]. The strains remain sensitiveness only to polymyxin.

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Basic Science

Mismatch Repair Proteins and Microsatellite Instability in Colorectal Carcinoma (MLH1, MSH2, MSH6 and PMS2): Histopathological and Immunohistochemical Study

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Keywords: Colorectal cancer; Immunohistochemistry; Lynch Syndrome; Microsatellite instability; Mismatch repair proteins.

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Abstract

BACKGROUND: Colorectal cancer (CRC) is one of the most common cancers worldwide. Microsatellite instability (MSI) is detected in about 15% of all colorectal cancers. CRC with MSI has particular characteristics such as improved survival rates and better prognosis. They also have a distinct sensitivity to the action of chemotherapy.

AIM: The aim of the study was to detect microsatellite instability in a cohort of colorectal cancer Egyptian patients using the immunohistochemical expression of mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2).

MATERIAL AND METHODS: Cases were divided into Microsatellite stable (MSS), Microsatellite unstable low (MSI-L) and Microsatellite unstable high (MSI-H). This Microsatellite stability status was correlated with different clinicopathological parameters.

RESULTS: There was a statistically significant correlation between the age of cases, tumor site & grade and the microsatellite stability status. There was no statistically significant correlation between the gender of patients, tumor subtype, stage, mucoid change, necrosis, tumor borders, lymphocytic response, lymphovascular emboli and the microsatellite stability status.

CONCLUSION: Testing for MSI should be done for all colorectal cancer patients, especially those younger than 50 years old, right sided and high-grade CRCs.

Introduction

Globally, more than one million people get colorectal cancer annually [1]. It is the second most common cause of cancer in women (after breast cancer) and the third most common in men (after lung and prostate cancers) [2].

In Egypt, there was a rapid increase in colorectal cancer incidence, where the occurrence was formerly low. Egypt reveals an unusually high rate of colorectal carcinoma under age 40, low prevalence of colorectal polyps in cancer patients and a predominant cancer site in the rectum [3].

Colorectal cancer is a heterogeneous disease, and so far four main molecular pathways have been identified. These four pathways are the Chromosomal Instability (CIN) Pathway, CpG Island Methylator Phenotype (CIMP) pathway, Microsatellite Instability (MSI) pathway and the Serrated pathway [4].

MSI is a kind of genomic instability that arises when mutations occur in nucleotide repeat sequences throughout the genome. These repeat sequences are known as microsatellites, and the discrepancy that arises between these sequences in tumor and germline cells is known as microsatellite instability [5]. MSI arises from defects in the DNA mismatch repair (MMR) system which corrects any errors made by DNA polymerases during the replication of DNA [6].

Lynch Syndrome (LS), previously termed hereditary non-polyposis colorectal cancer, is an inherited condition of defective DNA MMR and predisposes people to a variety of cancers [7]. Colorectal cancer is the most common type of cancer associated with Lynch syndrome [8].

LS is caused by autosomal dominant heterozygous germline mutations in one of the four key MMR genes — the mutL homologue 1 (*MLH1)*(chromosome 3p21.3),mutS homologue 2*(MSH2)*(chromosome 2p22–21), mutS homologue 6 (*MSH6)*(chromosome 2p16) or postmeiotic segregation increased 2 *(PMS2)*(chromosome 7p22.2) genes [9].

The loss of function occurs due to a germline mutation in one allele of one of the DNA- MMR genes; however, inactivation of the second allele, which is mostly acquired, is needed for the development of cancers [10].

MSI sporadic CRCs were found to be caused primarily by somatically acquired hypermethylation of both alleles of the MLH1 promoter, with resultant loss of MLH1 protein expression, which was closely associated with the presence of the oncogenic BRAFV600E mutation [11].

The DNA-MMR enzymes work in pairs (dimers- MLH1/PMS2 and MSH2/MSH6), and formation of the complex is important for their stability. When a MLH1 function is lost, immunoreactivity for PMS2 disappears. The same happens with MSH6; when the MSH2 function is lost. However, when the PMS2 orMSH6 function is lost, MLH1 and MSH2 find other MMR partners and hence appear partially preserved on immunohistochemistry [12].

Testing tumors for MSI by immunohistochemistry for MMR proteins and/or by molecular-based methods is routinely performed for patients diagnosed with colorectal carcinoma, primarily to screen for Lynch syndrome. Up to 15% of all colorectal carcinomas demonstrate MSI, more frequently secondary to acquired methylation of MLH1 (sporadic cases) than caused by a germline mutation (Lynch syndrome) [5].

From a clinical point of view, MSI-high (MSI-H) tumors as compared with microsatellite stable (MSS) ones, are diagnosed at a younger age, with a predominance in the right colon, frequently raised from sessile serrated adenoma and are diagnosed at an earlier stage [13].

Mucinous cells, signet-ring cells and poorly differentiated cells are uncommon histologic types and are commonly observed in cancers with MSI-H [14]. Patients with MSI-positive tumors tend to have a better prognosis and are less likely to be associated with distant metastasis [15, 16].

The aim of the study was to detect microsatellite instability in a cohort of colorectal cancer Egyptian patients using the immunohistochemical expression of mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2).

Material and Methods

Fifty-two cases of colorectal cancer were retrieved from the pathology department, Ahmed Maher teaching hospital, Cairo, Egypt during the period from January 2012 to December 2015. Demographic and clinical data of the patients were collected from the hospital files.

Five thick sections were cut from Formalin-fixed paraffin embedded tissue blocks and stained with Hematoxylin and eosin for routine histopathological examination and determination of tumor type, grade, stage of the tumor and reporting co-findings such as; areas of tumor necrosis, presence or absence of lymphovascular invasion and lymphocytic response. Mucinous carcinoma was diagnosed if > 50% of the lesion was composed of mucin. Signet ring cell carcinoma was diagnosed if > 50% of tumor cells showed prominent intracytoplasmic mucin. Otherwise gland forming tumors without specific morphology were diagnosed as adenocarcinoma, NOS.

Immunohistochemical staining was performed using immunostainer (Shandon Sequenza) using the labeled streptavidin biotin method with the following reagents: Diva Decloaker, pretreatment antigen – retrieval, (Biocare Medical Catalog number: DV2004 LX, MX), Hydrogen peroxide block (Lab Vision, USA, Catalog number: TA-060-HP), Ultravision large volume detection system (Lab Vision, USA, Catalog number: TP-060- HL) including Ultra V Block, Biotinylated goat anti -polyvalent plus (link) & Streptavidin peroxidase plus (label) and DAB plus substrate system (Lab Vision, USA, Catalog number: TA-060-HDX) including DAB plus chromogen & DAB plus substrate.

The primary antibodies were PMS-2: a mouse polyclonal antibody (Biocare Medical Catalog number: PM 344 AA), MLH-1: a mouse monoclonal antibody (Biocare Medical Catalog number: PM 220 AA), MSH-6: a mouse monoclonal antibody (Biocare Medical Catalog number: PM 265 AA) and MSH-2: a mouse monoclonal antibody (Biocare Medical Catalog number: PM 219 AA).

Non-neoplastic colonic mucosa, stromal cells, infiltrating lymphocytes or the centres of lymphoid follicles, were used as positive internal controls. Sections of the same tissue were used following the same procedure, but the PBS was used instead of the primary antibody were used as negative internal controls.

Cases were categorised into positive (nuclear staining within tumor cells) and negative (complete absence of nuclear staining within tumor cells with concurrent internal positive controls) [17].

Then cases were interpreted as Microsatellite

stable (MSS) when all the four antibodies show positive nuclear staining of the tumor cells, as Microsatellite unstable low (MSI-L) when one antibody shows negative nuclear staining of the tumor cells (Fig. 1) and as Microsatellite unstable high (MSI-H) when two antibodies or more show negative nuclear staining of the tumor cells (Fig. 2) [18].

Statistical analyses were performed using Statistical Package for Social Science (SPSS 17.0 for Windows; SPSS Inc, Chicago, IL, 2010). Chi-Square test was used to examine the variable. P-value is significant when ≤ 0.05.

Results

The patients' age ranged from 27 to 87 years with a mean age of 55.86 ± 13.11 years with a male: female ratio ~1:1. 82.7% of cases were adenocarcinomas, NOS, 9.6% were a mucinous carcinoma, and 7.7% were signet ring cell carcinoma.

Both MLH-1 and PMS-2 were positive in 61.5% of cases, both were lost in 30.8%, and PMS-2 loss without MLH-1 loss was seen in 7.7%. Both of MSH-2 and MSH-6 were positive in 94.2% of cases, while the loss of MSH-6 without MSH-2 loss was seen in 5.8%. Accordingly; 57.7% of cases were MSS, 11.5% were MSI-L, and 30.8% were MSI-H.

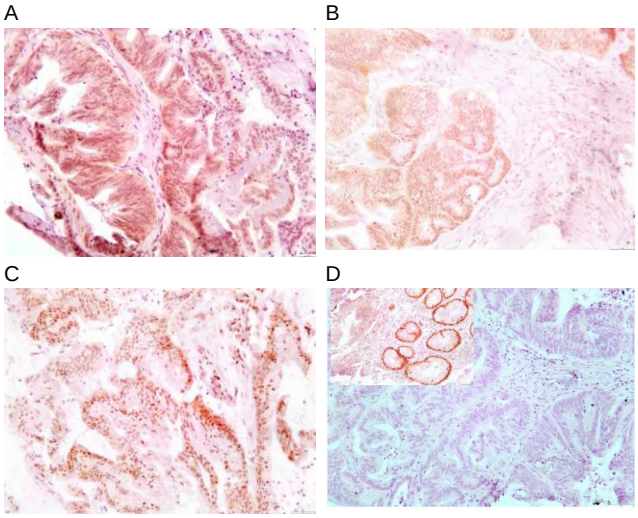

Figure 1: Immunohistochemical staining pattern of an MSI-L colorectal carcinoma with intact staining of MLH1 (A), PMS2 (B) and MSH2 (C) and isolated loss of MSH6 (D) with positive internal control (Upper left of D)

On the correlation of the stability status with the clinicopathological parameters, there was a statistically significant correlation between patients' age and microsatellite stability status; older age (≥ 50 years), was associated with MSS status while younger age (< 50 years), was associated with MSI-H status. Also, MSI-L status was seen only in older age (P value = 0.034). Also, there was a statistically significant correlation between tumor site and microsatellite stability status, where the left and transverse colon tumors tend to be MSS, while right colon tumors tend to be MSI-H (P-value = 0.014).

A significant relationship was found between tumor grade and microsatellite stability status after adding the MSS to MSI-L cases; MSS and MSI-L tumors tend to be low grade, while MSI-H tumors tend to be high grade. (P value= 0.025).

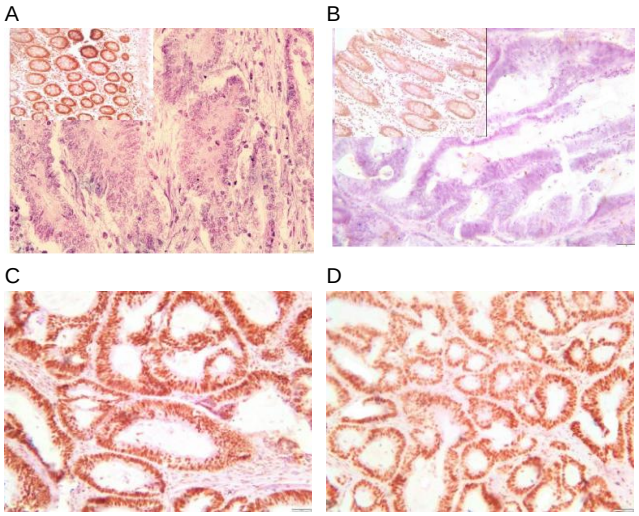

Figure 2: Immunohistochemical staining pattern of an MSI-H colorectal carcinoma with loss of both MLH1 (A) & PMS2 (B) with positive internal control (Upper left of A, B) and intact staining of MSH2 (C) & MSH6 (D)

An insignificant correlation between the microsatellite stability status and patients' sex, tumor subtype, tumor borders, tumor necrosis, lymphocytic response, lymphovascular emboli, T stage or lymph node status was found (Table 1).

Table 1: Descriptive Statistics of clinicopathological parameters and microsatellite stability status of CRC cases

		MSS n (%)	MSI-L n (%)	MSI-H n (%)	Total n (%)	P value
Age	< 50	9 (17.3)	0 (0)	9 (17.3)	18 (34.6)	0.034
	≥ 50	21 (40.4)	6 (11.5)	7 (13.5)	34 (65.4)	
Gender	Male	16 (30.8)	2 (3.8)	9 (17.3)	27 (51.9)	0.614
	Female	14 (26.9)	4 (7.7)	7 (13.5)	25 (48.1)	
Tumor site	Lt colon	22 (42.3)	5 (9.6)	5 (9.6)	32 (61.5)	0.014
	Rt colon	6 (11.5)	1 (1.9)	11 (21.2)	18 (34.6)	
	Transverse	2 (3.8)	0 (0)	0 (0)	2 (3.8)	
Tumor type	Adenocarcinoma.	25 (48.1)	6 (11.5)	12 (23.1)	43 (82.7)	0.729
	Mucinous ca	3 (5.8)	0 (0)	2 (3.8)	5 (9.6)	
	Signet ring ca	2 (3.8)	0 (0)	2 (3.8)	4 (7.7)	
Tumor grade	Low	29 (55.8)		8 (15.4)	37 (71.2)	0.025
	High	7 (13.5)		8 (15.4)	15 (28.8)	
Mucoid change	Present	10 (19.2)	2 (3.8)	5 (9.6)	17 (32.7)	0.989
	Absent	20 (38.5)	4 (7.7)	11 (21.2)	35 (67.3)	
Tumor necrosis	Present	13 (25)	2 (3.8)	8 (15.4)	23 (44.2)	0.773
	Absent	17 (32.7)	4 (7.7)	8 (15.4)	29 (55.8)	
Tumor border	Infiltrative	18 (34.6)	3 (5.8)	11 (21.2)	32 (61.5)	0.698
	Pushing	12 (23.1)	3 (5.8)	5 (9.6)	20 (38.5)	
Lymphocytic response						
	Mild	20 (38.5)	3 (5.8)	11 (21.2)	34 (65.4)	0.789
	Moderate	8 (15.4)	3 (5.8)	4 (7.7)	15 (28.8)	
	Marked	2 (3.8)	0 (0)	1 (1.9)	3 (5.8)	
Vascular emboli	Present	17 (32.7)	2 (3.8)	7 (13.5)	26 (50)	0.484
	Absent	13 (25)	4 (7.7)	9 (17.3)	26 (50)	
T stage	T1+T2	2 (3.8)	1 (1.9)	3 (5.8)	6 (11.5)	0.434
	T3+T4	28 (53.8)	5 (9.6)	13 (25)	46 (88.5)	
N stage	N0	10 (19.2)	5 (9.6)	8 (15.4)	23 (44.2)	0.078
	N1	14 (26.9)	0 (0)	3 (5.8)	17 (32.7)	
	N2	6 (11.5)	1 (1.9)	5 (9.6)	12 (23.1)	

Discussion

Colorectal cancer is a common malignancy. It is the fourth most common cause of cancer death after lung, stomach and liver cancer [2]. It is not uncommon among Egyptian patients and rates are higher in patients under 40 years of age [19].

CRC shows a significant heterogeneity in both prognosis and response to therapy, even within the same pathological stage. This clinical heterogeneity may be in part linked to genetic alterations occurring during the pathogenesis [20].

MSI represents a molecular hallmark of Lynch syndrome. Nevertheless, the majority of cases with MSI are sporadic, more often due to an epigenetic inactivation of hMLH1 [21].

Concerning the microsatellite stability status of the cases in this study, a significant relation was found between the microsatellite stability status and patients' age, where older age is associated MSS status, and the younger age is associated with MSI-H status. This result is the same as that of Huang et al. [22] andof Yuan et al. [17]. Also, Jenkins et al. [23] and Greenson et al. [24] found that age under 50 years is a strong predictor of MSI.

Table 2: Summary of other studies findings regarding clinicopathological parameters related to MSI-H

	Parameters related to MSI-H
Faghani et al. [25]	Left colon
Frey et al. [26]	Right colon and high grade
Greenson et al. [24]	Young age, right colon, high grade and mucinous differentiation
Huang et al. [22]	Young age, right colon, low grade and mucinous differentiation
Jenkins et al. [23]	Young age, right colon, high grade and mucinous differentiation
Joel et al. [28]	Low grade
Raut et al. [13]	High grade and mucinous differentiation
Yearsley et al. [27]	High grade and mucinous differentiation
Yuan et al. [17]	Young age

On the contrary, Faghani et al. [25] found that there was no a statistically significant correlation between MSI and patients' age, this can be explained by that their study was designed to determine the correlation between MSI and sporadic cases only.

A significant relationship was found between the microsatellite stability status and tumor site where the left and transverse colon tumors tend to be MSS while right colon tumors tend to be MSI-H. Also, Huang et al. [22] and Frey et al. [26] found the same. Jenkins et al. [23] and Greenson et al. [24] found that right location was also a strong predictor of MSI.

On the contrary, Faghani et al. [25] found that 81.8% of total MSI-H had distal tumors. This is may be due to studyng only sporadic cases and analysis of MSI frequencies by testing the BAT-26 and BAT-25 markers.

Also, a significant relation was found between microsatellite stability status and the tumor grade, where MSS and MSI-L tumors tend to be low grade, while MSI-H tumors tend to be high grade. This is the same as Raut et al. [13], Yearsley et al. [27] and Frey et al. [26] results. Jenkins et al. [23] and Greenson et al. [24] found that poor or undifferentiated histology is a strong predictor of microsatellite instability.

On the contrary, Joel et al. [28] found that the presence of well-differentiated tumors were important markers for microsatellite instability. Also, Huang et al. [22] found that MSI-H tumors were more likely to show less local aggressiveness and lower differentiation. These results may be due to the difference in the genetic and hereditary background among their patients and the Egyptian patients included in this study and use of molecular analyses besides the immunohistochemical tests.

Although no significant relationship could be found in our study between the microsatellite stability status and tumor subtype or mucin presence, a great production of mucin with extracellular accumulation often correlates with MSI [29]. This discrepancy is due to the small number of mucinous and signet ring cell carcinoma cases in our study. Yearsley et al. [28] found the percentage of mucin differed significantly between MSI-H and MSI-L or MSS. Also, Raut et al. [13] and Huang et al. [22] found that MSI is associated with a mucinous histology. Jenkins et al. [23] and Greenson et al. [24] found that signet ring or focal signet ring differentiation and mucinous or focal mucinous differentiation were statistically significant predictors of microsatellite instability.

In conclusion, our study showed a statistically significant correlation between patients' age, tumor site and grade and the microsatellite stability status. It is recommended that testing for MSI is done for all colorectal cancer patients younger than 50 years old, right sided and high-grade tumors. Further studies on a larger number of patients should be done to study the relation between MSI and other pathological parameters.

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Clinical Science

Neutrophil to Lymphocyte Ratio, Platelet to Lymphocyte Ratio, Mean Platelet Volume and Red Cell Distribution Width Measures in Bells Palsy

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Keywords: Facial paralysis; inflammatory marker; neutrophil; neutrophil-to-lymphocyte ratio.

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Abstract

AIM: The purpose of this study was to investigate the usefulness of the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) Mean Platelet Volume (MPV) and Red Cell Distribution Width (RDW) in the differential diagnosis and follow-up of patients with Bells Palsy.

MATERIAL AND METHODS: Twenty-eight patients diagnosed with Bells Palsy and 28 control patients were included in the study. Serum samples were analysed retrospectively on the initial presentation and the seventh day of admission.

RESULTS: On admission, the NLR was 1.7±1.2. The mean absolute neutrophil count was 6100 ± 900/mm^3 in Bells Palsy Group. NLR was 0.9 ± 0.2. The mean absolute neutrophil count was 4400 ± 1100/mm^3 in control group. Statistically, significant changes were not observed in NLR, PLR, MPV and RDW measurements in Bells Palsy group between House-Brackman Staging.

CONCLUSION: Statistically significant changes in the neutrophil count and NLR were determined in the measurements between Bells Palsy and control group (p = 0.013, p = 0.016 respectively) on admission. A grade of the disease and NLR measurements had no statistically significant connection. RDW value was investigated for the first time in the literature for Bells Palsy patients.

Introduction

Bells palsy (idiopathic facial paralysis) is the most common cause of unilateral peripheral facial paralysis. The incidence of the disease is 11-40/100,000 in the literature [1]. Vascular causes, autoimmune diseases and inflammation of the nerve sheath can be the etiological factors of the disease [1].

The neutrophil to lymphocyte ratio (NLR) is a useful marker that demonstrates the general inflammation condition. The presence of an elevated NLR was demonstrated in a follow-up of inflammatory diseases like larynx cancer, chronic hepatitis, Behcet's disease, Celiac disease and ulcerative colitis [2-4].

Platelet to lymphocyte ratio (PLR) can be used in the follow-up of inflammation and cancer diseases like peripheral vascular system disorders, coronary artery disease, gynecologic and hepatobiliary system malignancies [5, 6].

Mean Platelet Volume (MPV) and Red Cell Distribution Width (RDW) are markers that can be used in general inflamatory and peripheric thrombotic disease in the literature [7]. There are no investigations about Bells Palsy and RDW measures in literature.

In the present study, we aimed to evaluate the NLR, PLR, MPV and RDW differences between the differential diagnosis and follow-ups of Bells Palsy patients. We aimed to investigate the whole markers that can be investigated from the simple blood test in Bells Palsy. RDW value was investigated for the first time in the literature for Bells Palsy patients.

Material and Methods

Patients admitted to the Sakarya Akyazi General Hospital between February 2013 and December 2015 with complaints about acute peripheral Bells Palsy were evaluated retrospectively. The study population comprised 28 patients diagnosed with Bells Palsy and 28 control patients.

Patients underwent general examination, with a neurological and otorhinolaryngological examination. Blood biochemistry and whole blood analysis were performed. Temporal Magnetic Resonance (MR) was performed on all members of the study population. The disease is staged using House-Brackman Staging system. 12 patients were Grade 2, ten patients were Grade 3, three patients were Grade 4 and three patients were Grade.

The exclusion criteria comprised the presence of an acute/chronic ear infection history, chronic liver failure, chronic inflammatory immunological disorders, neurological diseases, diabetes mellitus, hypertension, chronic renal failure, acute coronary artery disease, active connective tissue disorder, vasculitis, inflammatory bowel disease and. Patients using drugs such as antidiabetic drugs, steroids, chemotherapy drugs, immunomodulatory drugs, antihistaminic drugs, sedative drugs and analgesics were also excluded. Peripheral venous sampling for whole blood analysis and blood biochemistry was performed between 08:00 and 10:00. Whole blood analyses were performed using the same device (ABOTT CELL DYN 3700). Whole blood analyses were performed on admission and the seventh day of the first control after a period of fasting lasting at least eight hours. Systemic neurological and otorhinolaryngological examinations were performed.

Whole blood analysis results were evaluated retrospectively. The NLR was calculated by dividing the neutrophil count by the lymphocyte count per microlitre (NLR = neutrophils (×10^3 per µl) ÷ lymphocytes (×10^3 per µl)). PLR ratio was calculated by dividing platelet count by the lymphocyte count per microlitre.

Statistical analysis was performed using SPSS, version 19.0 for Windows (IBM, Armonk, NY). Descriptive data were expressed as means and standard deviation. The Kolmogorov-Smirnov test was used for a normality test. Mann-Whitney-U tests were used to evaluate differences between the groups. The Wilcoxon test was used to evaluate differences between whole blood count parameters on admission, and on the seventh day of admission, within groups Pearson, correlation analysis was used to evaluate differences between House-Brackman Staging system and parameters. For each test, a P value of 0.05 or less was treated as statistically significant.

Results

Twenty-eight patients were included in the study (16 males (57%), 12 females (43%). The mean age was 29.5 ± 10.5 (18–62).

Table 1: Haemogram parameters of patients with Bells Palsy

	Admission (Mean ± Std. Dev.)	1st Week (Mean ± Std. Dev.)	P
Haemoglobin (g/dl)	12.4 ± 0.7	12.9 ± 0.6	0.12
Haematocrit (%)	37.8 ± 4.2	37.0 ± 4.2	0.66
Neutrophil (K/µl)	6.1 ± 0.9	5.9 ± 0.9	0.304
Lymphocyte (K/µl)	3.8 ± 1.2	3.0 ± 0.8	0.376
NLR	1.7 ± 1.2	1.5 ± 0.9	0.07
PLR	129.4 ± 15.4	135.2 ± 19	0.07
MPV (fL)	8.2 ± 0.4	8.4 ± 0.3	0.6
RDW (%)	12.9 ± 0.6	12.2 ± 0.4	0.7

Mean ± Std. Dev: Mean ± Standard Deviation, WBC: White Blood Cell, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, MPV: Mean Platelet Volume, RDW; Red Cell Distribution.

Socio-demographic data and the entire blood results of the Bells Palsy population are demonstrated in Table 1. On admission, the NLR was 1.7 ± 1.2 (Fig. 1). The mean absolute neutrophil count was 6100 ± 900/mm^3, and the mean absolute lymphocyte count was 3800 ± 1200/mm^3. PLR was 129.4 ± 15.4; MPV was 8.2 ± 0.4 fL and RDW was 12.9 ± 0.6 on admission. On the seventh day of admission, the NLR was 1.5 ± 0.9. The mean absolute neutrophil count was 5900 ± 900/mm^3, and the mean absolute lymphocyte count was 3000 ± 800/mm^3. PLR was 135.2 ± 19, MPV was 8.4 ± 0.3 fL and RDW was 12.2 ± 0.4 (Table 1).

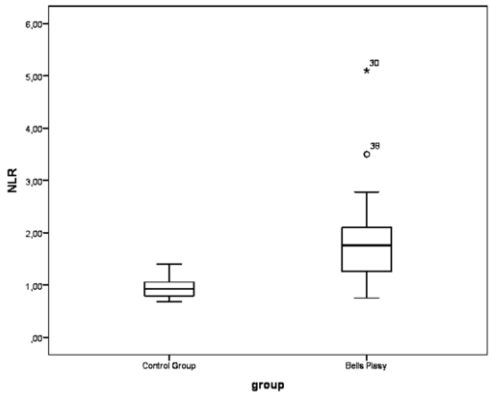

Figure 1: NLR and Bells Palsy can be seen on Figure(NLR: Neutrophil to Lymphocyte Ratio)

On admission, NLR was 0.9 ± 0.2, the mean absolute neutrophil count was 4400 ± 1100/mm^3, and the mean absolute lymphocyte count was 3900 ± 1200/mm^3. PLR was 139.4 ± 19.4; MPV was 8.4 ± 0.4 fL and RDW was 12.5 ± 0.6 on a control group. On the seventh day of admission, NLR was 1.1 ± 0.1, the mean absolute neutrophil count was 4100 ± 300/mm^3, and the mean absolute lymphocyte count was 4000 ± 600/mm^3. PLR was 134.2 ± 12, MPV was 8.1 ± 0.3 fL and RDW was 12.1 ± 0.4 (Table 2).

Table 2: Haemogram parameters of control patients

	Admission (Mean ± Std. Dev.)	1st Week (Mean ± Std. Dev.)	P
Haemoglobin (g/dl)	13.5 ± 0.4	13.2 ± 0.9	0.08
Haematocrit (%)	37.8 ± 4.4	38 ± 3.4	0.92
Neutrophil (K/μl)	4.4 ± 1.1	4.1 ± 0.3	0.3
Lymphocyte (K/μl)	3.9 ± 1.2	4 ± 0.6	0.4
NLR	0.9 ± 0.2	1.1 ± 0.1	0.2
PLR	139.4 ± 19.4	134.2 ± 12	0.07
MPV (fL)	8.4 ± 0.4	8.1 ± 0.3	0.6
RDW (%)	12.5 ± 0.6	12.1 ± 0.4	0.7

Mean ± Std. Dev: Mean ± Standard Deviation, WBC: White Blood Cell, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, MPV: Mean Platelet Volume, RDW; Red Cell Distribution.

Statistically significant changes between the neutrophil count, the lymphocyte count, NLR, PLR, MPV and RDW were not determined using the measurements made in the one week interval between examinations of the Bells Palsy group (p = 0.3, p = 0.37, p = 0.2, p = 0.07, p = 0.6, and p = 0.7, respectively) (Table 2).

Statistically, significant changes in the neutrophil count and NLR were determined in the measurements between Bells Palsy and control group (p = 0.013, p = 0.016 respectively) on admission (Table 3). There is still statistically significant difference on 7. Day of admission (p = 0.016, p = 0.03 respectively).

Table 3: Comparison of haemogram parameters between patients with patients and control group

	Admission (Mean ± Std. Dev.)		P	1st Week (Mean ± Std. Dev.)		P
	BellsPalsy	Control		BellsPalsy	Control	
Haemoglobin	12.4 ± 0.7	13.5 ± 0.4	0.203	12.9 ± 0.6	13.2 ± 0.9	0.635
Haematocrit	37.8 ± 4.2	37.8 ± 4.4	0.677	37 ± 4.2	38 ± 3.4	0.828
Neutrophil (K/μl)	6.1 ± 0.9	4.4 ± 1.1	0.013	5.9 ± 0.9	4.1 ± 0.3	0.016
Lymphocyte (K/μl)	3.8 ± 1.2	3.9 ± 1.2	0.42	3 ± 0.8	4 ± 0.6	0.3
NLR	1.7 ± 1.2	0.9 ± 0.2	0.0016	1.5 ± 0.9	11.1 ± 0.1	0.03
PLR	129.4 ± 15.4	139.4 ± 19.4	0.65	135.2 ± 19	134.2 ± 12	0.8
MPV (fl)	8.2 ± 0.4	8.4 ± 0.4	0.67	8.4 ± 0.3	8.1 ± 0.3	0.6
RDW (%)	12.9 ± 0.6	12.5 ± 0.6	0.8	12.2 ± 0.4	12.1 ± 0.4	0.7

Mean ± Std. Dev: Mean ± Standard Deviation, WBC: White Blood Cell, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, MPV: Mean Platelet Volume, RDW; Red Cell Distribution.

Significant changes were not observed in haemoglobin and haematocrit values, lymphocyte counts, PLR, MPV and RDW measurements between Bells Palsy and control Group (p = 0.2, p = 0.67, p = 0.42, p = 0.65, p = 0.67, p = 0.8 respectively) on first admission. There is still no significant change on 7, day of admission between groups.

Table 4: The distribution of NLR and mean PLR by the patient groups divided according to House-Brackmann Grading of Paralysis

Paralysis grade	Number of patients	NLR	PLR	MPV	RDW
2	12	1.7 ± 1.2	129.4 ± 15.4	8.2 ± 0.4	12.9 ± 0.6
3	10	1.6 ± 1.3	130.4 ± 15.2	8.1 ± 0.4	12.8 ± 0.5

Mean ± Std. Dev: Mean ± Standard Deviation, WBC: White Blood Cell, NLR: Neutrophil to Lymphocyte Ratio, PLR: Platelet to Lymphocyte Ratio, MPV: Mean Platelet Volume, RDW; Red Cell Distribution.

Significant changes were not observed in NLR, PLR, MPV and RDW measurements in Bells Palsy group between House-Brackman Staging (p = 0.84, p = 0.79, p = 0.63, p = 0.64 respectively). A grade of the disease and NLR measurements had no statistically significant connection.

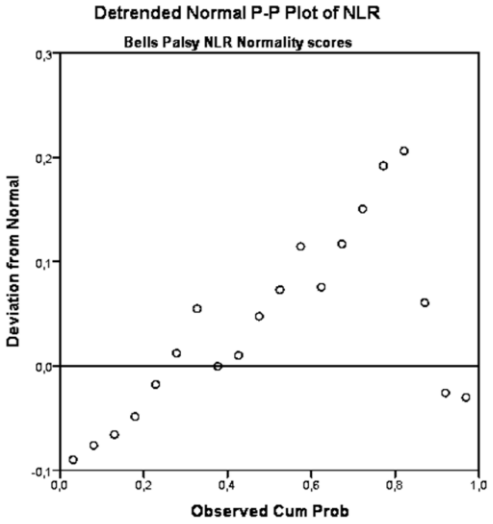

Figure 2: Normality scores of NLR in Bells Palsy patients

Discussion

The most important outcome of the present study was that the NLR and neutrophil count was significantly higher in patients with Bells Palsy than in control Group; this ratio was higher in the Bells Palsy than in the control group in the first week after admission. The second most important result of this study was the demonstration of statistically not significant changes on PLR; MPV; RDW measurements. The third important result of the study is there is no significant change in measures between House-Brackman classifications of Bells palsy. Therefore the NLR value does not change in the different grades of disease.

There were several causative aetiological factors for Bells Palsy. Viral infections and inflammation, vascular neuritis, peripheral vascular diseases, thromboembolism and microvascular circulatory impairment, immunological diseases were known factors [1]. Viruses were the most common aetiological factors, but it is not enough to determine the whole aetiology. From the microvascular circulatory impairment point of view, neuritis was associated with vascular inflammation.

Whole blood analysis is associated with the general condition of the patient. Higher neutrophil counts can be associated with inflammatory conditions. Lower lymphocyte count can be associated with higher organic stress [3]. The NLR is an inflammatory marker that has been studied in

recent years, for the differential diagnosis and follows up of certain diseases. The NLR was evaluated in, acute hearing loss, Bell's palsy and vertigo in the practice of Otorhinolaryngology [8, 9]. The NLR as an inflammatory marker was shown to be associated with the prognosis of cancer of the body [10].

The presence of an elevated NLR in Bells Palsy was demonstrated via the literature search [11-13]. NLR ratio was higher in 656 patients Bells Palsy group in a study [12]. NLR was also higher in Bells patients and another study by Ozler et al. NLR measurements were correlated with the disease in this study [13]. Atan et al. (2015) revealed that NLR was higher in 99 Bells palsy group, but the NLR was not correlated with House-Brackman grade [14]. Eryılmaz et al. (2015) revealed that NLR was higher in paediatric Bells palsy group, but the NLR was not correlated with House-Brackman grade [11]. There was no consensus on literature about the correlation of NLR and grade of the disease in the literature.

MPV is a parameter indicating platelet volume. It can be correlated with microvascular thrombotic diseases. MPV correlation with stroke is revealed in the literature [15]. In this perspective, MPV can be associated with microvascular obstruction. Correlation with MPV levels and Bells palsy was not documented in the literature [12]. In our study MPV was no statistically significantly higher in Bells patients.

RDW is a parameter indicating height and heterogeneity of the erythrocyte volume [16]. This parameter can increase in anaemia, myelodysplastic syndromes, haemolytic diseases and cause microvascular thrombotic diseases [16]. Correlation of RDW and migraine is posted in the literature [17]. Also, there are studies about the relation of RDW with coronary diseases in the literature [18, 19]. There is no actual study about RDW and Bells palsy in the literature. In our study RDW was no statistically significantly higher in Bells palsy patients.

PLR is also a parameter used as NLR widely in the literature nowadays. There are studies that have been done with the values PLR in the myocardial infarct [20]. PLR is posted in gastric and oesophagal cancer in the literature [21]. PLR is associated with sudden hearing loss in the literature [8]. There are few investigations about Bells Palsy and PLR in literature. In our study PLR was no statistically significantly higher in Bells palsy patients.

The limitations of our study were the retrospective design of the study, the limited number of cases and the limited time available for the second evaluation. Further prospective studies to evaluate the association between the NLR and both the diagnosis and prognosis of Bells palsy are needed.

In the present study, the NLR and neutrophil count were significantly higher in patients with Bells Palsy than in those with a control group. There is statistically significant change between NLR and Grade of the disease. Our study strengthened the inflammation theory as an aetiological factor for Bells Palsy rather than ischemic theory. Factors can be associated with peripheral vascular diseases and thromboembolism such as PLR, MPV, and RDW was normal in our study regarding control group. We aimed to investigate the whole blood parameters in Bells Palsy to evaluate the mean and connection with Bells Palsy herein.

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Obstructive Sleep Apnea and Lipid Abnormalities

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Abstract

BACKGROUND: There has been a great interest in the interaction between obstructive sleep apnea (OSA) and metabolic dysfunction, but there is no consistent data suggesting that OSA is a risk factor for dyslipidemia.

AIM: The aim of this cross-sectional study was to evaluate the prevalence of lipid abnormalities in patients suspected of OSA, referred to our sleep laboratory for polysomnography.

MATERIAL AND METHODS: Two hundred patients referred to our hospital with suspected OSA, and all of them underwent for standard polysomnography. All patients with respiratory disturbance index (RDI) above 15 were diagnosed with OSA. In the morning after 12 hours fasting, the blood sample was collected from all patients. Blood levels of triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL), were determined in all study patients. In the study, both OSA positive and OSA negative patients were divided according to the body mass index (BMI) in two groups. The first group with BMI ≤ 30 kg/m^2 and the second group with BMI > 30 kg/m^2.

RESULTS: OSA positive patients with BMI ≤ 30 kg/m^2 had statistically significant higher levels of triglycerides and total cholesterol, and statistically significant lower level of HDL compared to OSA negative patients with BMI ≤ 30. There were no statistically significant differences in age and LDL levels between these groups. OSA positive patients with BMI > 30 kg/m^2 had higher levels of triglycerides, total cholesterol and LDL and lower levels of HDL versus OSA negative patients with BMI > 30 kg/m^2, but without statistically significant differences.

CONCLUSION: OSA and obesity are potent risk factors for dyslipidemias. OSA could play a significant role in worsening of lipid metabolism in non-obese patients. But in obese patients, the extra weight makes the metabolic changes of lipid metabolism, and the role of OSA is not that very important like in non-obese patients.

Introduction

Obstructive sleep apnea (OSA) is an increasingly prevalent condition that is characterised by repetitive upper airway obstructions resulting in intermittent hypoxia and sleep fragmentation caused by arousals [1]. Among adults, 30–70 years of age, approximately 13% of men and 6% of women, have moderate to severe forms of OSA [2]. OSA is often closely associated with other conditions which are recognised causes of morbidity and mortality such as obesity, metabolic syndrome, atherosclerosis, systemic inflammation, insulin resistance and type 2 diabetes mellitus [3, 4]. Recently, there has been a great interest in the interaction between OSA and metabolic dysfunction. There is no consistent data suggesting that OSA is a risk factor for dyslipidemia. Indeed, conflicting results have been observed in cross-sectional and interventional studies [5]. Taking into account components of the metabolic syndrome, some reports found increased levels of triglycerides [6-9] and reduced levels of high-density lipoproteins (HDL) in patients with OSA [8-10], while others studies did not find the correlation between OSA and dyslipidemia [11,12]. Of note, the majority of the studies were not specifically designed to evaluate the lipid profile. Therefore, more evidence is still needed.

Increased understanding of the independent associations between OSA, metabolic syndrome and insulin resistance is important to develop appropriate therapeutic strategies to reduce the high cardiometabolic risks in patients with OSA.

The aim of this cross-sectional study was to evaluate the prevalence of lipid abnormalities in patients suspected for OSA referred to our sleep laboratory for polysomnography.

Material and Methods

The study included 200 patients. It was conducted at University Clinic of Pulmonology and Allergy in Skopje. Inclusion criteria for patients were age from 35 to 60 years and persistence of minimum 2 of 3 clinical symptoms of OSA. The symptoms were snoring, witnessed apnea and daytime sleepiness. Exclusion criteria were previous history and treatment of diabetes and lipid abnormalities.

The study was approved by Ethical Committee of the Faculty of Medicine with No. 03-941/2, and before the study procedures, informed consent was obtained from all patients. Body mass index (BMI) was calculated, and patients were divided into two groups according to the BMI. All patients underwent polysomnography (Respironix, model Alice 5). All results from polysomnography were scored manually according to standard criteria [13]. Apnea, hypopnea and arousals were also identified according to the standard criteria and summarised in the form of a respiratory disturbance index (RDI). All patients with RDI above 15 were diagnosed with OSA.

In the morning after 12 hours fasting, a blood sample was collected from all patients. Blood levels of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL), were assessed. Biochemical measurements were conducted using an Architect Abbott C8000 auto analyser.

Statistical analyses were performed using Statistical software (Stat Soft). Data were expressed as *mean (X)* and *standard deviation (SD)*. Comparisons between variables were made using the unpaired t test for parametric data. The multiple linear regressions were used to determine the association between OSA and metabolic parameters. Statistical significance was considered at p less than 0.05.

Results

From all study patients, 51 were female with an average age of 49 ± 9 years, and 149 were men average age of 47 ± 9 years. There was no significant difference in age, BMI and RDI between male and female. There was the significant difference in the occurrence of OSA in men versus women, 109 (73.2%) of males and 31 (62.8%) of females were OSA positive ($p < 0.03$).

According to BMI, patients in the study were divided into two groups. There were 120 non-obese patients with BMI ≤ 30 kg/m^2, and 80 obese patients with BMI > 30 kg/m^2. In a non obese group with BMI ≤ 30, 62 patients were OSA negative and 58 patients were OSA positive. In an obese group with BMI > 30, 14 patients were OSA negative, and 66 patients were OSA positive (Figure 1).

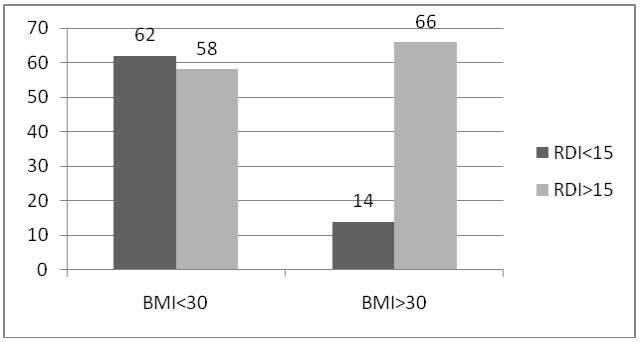

Figure 1: Frequency of OSA in study patients divided according to BMI. RDI = Respiratory disturbance index; BMI = Body mass index

OSA patients had statistically significant higher BMI, triglycerides, total cholesterol and lower HDL when compared to OSA negative patients (Table 1). There was no statistical difference in age and LDL levels between these two groups of patients.

Table 1: Comparison between OSA positive and OSA negative patients

	OSA negative RDI < 15 (76 patients)		OSA positive RDI > 15 (124 patients)		
	X	SD	X	SD	P
RDI	5.04	3.81	43.78	18.71	0.000
Age (years)	47.29	9.73	48.22	8.49	NS
BMI (kg/m^2)	27.58	3.14	31.11	4.35	0.000
TG (mmol/l)	1.60	0.36	1.76	0.26	0.000
TC (mmol/l)	4.94	0.50	5.22	0.34	0.000
HDL (mmol/l)	1.45	0.23	1.34	0.23	0.001
LDL (mmol/l)	2.85	0.53	2.94	0.49	NS

OSA = Obstructive sleep apnea; RDI = Respiratory disturbance index; BMI = Body mass index; TG = Triglycerides; TC = Total cholesterol; HDL= High-density lipoprotein cholesterol; LDL = Low-density lipoprotein cholesterol.

In the study, both OSA positive and OSA negative patients were divided according to BMI in two groups, first group with BMI ≤ 30 and the second group with BMI > 30. OSA positive patients with BMI ≤ 30 had statistically significant higher levels of triglycerides and total cholesterol, and statistically significant lower level of HDL compared to OSA negative patients with BMI ≤ 30. There were no statistically significant differences in age and LDL levels between these groups (Table 2).

Table 2: Comparison between OSA positive and OSA negative patients with BMI ≤ 30

	BMI ≤ 30				
	RDI < 15 (62 patients)		RDI > 15 (58 patients)		
	X	SD	X	SD	p
RDI	4.65	3.41	38.68	16.92	0.000
Age (years)	47.08	9.56	47.62	8.38	NS
BMI (kg/m^2)	26.55	2.40	27.38	1.80	0.035
TG (mmol/l)	1.53	0.28	1.66	0.18	0.003
TC (mmol/l)	4.90	0.49	5.10	0.28	0.010
HDL (mmol/l)	1.55	0.22	1.35	0.19	0.000
LDL (mmol/l)	2.84	0.52	2.79	0.36	NS

RDI = Respiratory disturbance index; BMI = Body mass index; TG = Triglycerides; TC = Total cholesterol; HDL= High-density lipoprotein cholesterol; LDL = Low-density lipoprotein cholesterol.

OSA positive patients with BMI>30 had higher triglycerides, total cholesterol and LDL and lower HDL versus OSA negative patients with BMI>30, but without statistically significant differences (Table 3.)

Table 3: Comparison between OSA positive and negative patients with BMI > 30

	BMI >30				
	RDI < 15 (14 patients)		RDI > 15 (66 patients)		
	X	SD	X	SD	p
RDI	6.81	5.01	48.26	19.17	0.000
Age (years)	48.21	10.76	48.74	8.62	NS
BMI (kg/m^2)	32.14	1.59	34.38	3.11	0.011
TG (mmol/l)	1.85	0.49	1.90	0.28	NS
TC (mmol/l)	5.12	0.53	5.33	0.35	NS
HDL (mmol/l)	1.37	0.25	1.30	0.23	NS
LDL (mmol/l)	2.94	0.60	3.08	0.55	NS

RDI = Respiratory disturbance index; BMI = Body mass index; TG = Triglycerides; TC = Total cholesterol; HDL= High-density lipoprotein cholesterol; LDL = Low-density lipoprotein cholesterol.

When all parameters were analysed with multiple linear regressions, only BMI, total cholesterol levels and LDL levels were found to be independent predictors of OSA (Table 4).

Table 4: Independent predictors of OSA

	OR	95%CI	p
BMI	1.6	1.39-1.83	0.000
TC	1.73	1.38-2.16	0.000
LDL	1.47	1.19-1.81	0.000

BMI = Body mass index; TC = Total cholesterol; LDL = Low-density lipoprotein cholesterol.

Discussion

OSA is the potent risk factor for metabolic disorders. The mechanisms through which OSA may worsen metabolism are complex. It may trigger several pathological mediating pathways (sympathetic activation, neurohumoral changes, glucose homoeostasis disruption, inflammation and oxidative stress) through chronic intermittent hypoxia (CIH), and these may ultimately cause deterioration in the metabolic function [14, 15]. According to previous studies, the prevalence of OSA is increased fourfold in patients with obesity. Obesity plays a major part in the development of the metabolic syndrome, which consists of insulin resistance, diabetes or impaired glucose tolerance, hypertension, and lipoproteinemia [16]. In this study, we have demonstrated that OSA positive patients had significantly higher level of triglycerides, total cholesterol and decreased HDL cholesterol levels versus OSA negative patients. LDL was also higher in OSA patients but with no significant value.

There were statistically significant differences in BMI between OSA positive and negative patients. So, the question is, does OSA affect lipid metabolism by itself or obesity is playing the major role in metabolic changes in these groups of patients. The relationships between OSA and various lipid parameters have not been extensively investigated like other components in the metabolic syndrome and the results have been more diverse. Studies of sleep clinic cohorts have consistently reported a higher prevalence of dyslipidemia in OSA positive subjects compared to those without OSA [17, 18].

The American Heart Health Sleep Study reported that apnea-hypopnea index (AHI) was inversely related to HDL-cholesterol levels in younger men and women, but not in older men, and triglyceride levels in younger men and women only [19]. In contrast, Lam et al. evaluated 255 patients between 30 and 60 years, and they did not find the association between OSA and HDL or TG levels, after controlling for confounding variables [20]. In our study, after dividing patients according to BMI, OSA positive patients with BMI < 30 had statistically significant higher levels of triglycerides and total cholesterol, and statistically significantly lower levels of HDL versus OSA negative patients with BMI ≤ 30. This result is corresponding with previously cited studies [6-8, 9, 17-19]. However, several studies that were searching for an association between metabolic syndrome and normal weight, over weight and obese patients, reported that prevalence of metabolic syndrome in non-obese patients (BMI 25.0-26.9 kg/m^2) is between 9.6-22.5%, depending on ethnicity and sex [21, 22]. So the possibility that OSA mechanisms are worsening lipid metabolism in a non obese group of patients is very high rather that weight gain. In obese patients, both OSA positive and OSA negative, there were no statistically significant differences in lipid blood levels. This result is corresponding with others studies. Sahin et al. in their study found out that OSA positive obese patients had statistically significant higher levels of lipids compared to OSA positive patients with normal weight. But in obese patients, both OSA positive and OSA negative, there were no statistically significant differences in blood levels of lipids [23]. Sharma et al. compared three groups of patients, 40 obese OSA positive patients, 40 obese OSA negative patients and 40 normal weight OSA negative patients and found that there was no difference in metabolic status between obese OSA positive and obese OSA negative patients [24]. Schäfer et al. found no relationship between OSA and concentration of lipoproteins in 81 male subjects [25]. Results from national surveys suggest that dyslipidemias are the most common comorbidities associated with a range of body mass indices (BMI),

with substantial increases found with increased body weight. It is estimated that about 68% of obese adults in the National Health and Nutrition Examination Survey population had metabolic abnormalities [26]. However, the limiting factor of this study may be not so large number of patients, particularly the small number of OSA negative patients with a BMI > 30. It should be noted that patients with previous history and treatment of diabetes and lipid disorders were excluded from the study.

In conclusion, OSA and obesity are the potent risk factor for dyslipidemias. OSA could play the significant part in worsening of lipid metabolism in non-obese patients. But in obese patients, the extra weight makes the metabolic changes of lipid metabolism, and the roll of OSA is not that very important like in non-obese patients.

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Aortic Annulus Enlargement: Early and Long-Terms Results

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Abstract

AIM: Patient-prosthesis mismatch (PPM) is a common occurrence in aortic valve surgery. Even the discussions about the impact of this phenomenon on the results of aortic valve surgery, the management of this problem remain one of the main topics in this kind of surgery. One of the ways of a solution is aortic annulus enlargement. The main topic of this study is to evaluate the early and longterm results of this technique in our country.

METHODS: During the period January 2010 –January 2015, 641 patients performed aortic valve surgery. In ten patients we performed aortic annulus enlargement according to Manouguian technique to avoid severe patient-prothesis mismatch. Operative mortality and perioperative complications (low cardiac output, pulmonary complications, etc..) were considered the indicators of the early results. Survival, clinical presentation according to NYHA, quality of life were the indicators to evaluate long-term results. Preoperative and postoperative echocardiographic data were also used to evaluate our results. We collected the data from hospital registrations and periodical clinical visit and echographic examination after hospital discharge.

RESULTS: In our group, 6 of 10 patients were diagnosed with stenotic aortic valve, two patients had aortic valve regurgitation and two mixed valve pathology. Four patients had concomitant cardiac surgery procedure, mitral or CABG. In all cases, aortic valve pathology was the primary diagnose.In the preoperative echocardiographic examination mean transvalvular gradient was 54.3 ± 6.42.We had no death during early or late postoperative period. Only one patient had pulmonary complications and long time of respiratory assistance because of his pulmonary pathology.The same patient had low cardiac output and wound infection. Early after surgery mean transprostethic gradient was 16.2 ± 3.44 and late postoperative was 15.9 ± 4.3. No patient had the severe patient-prothesis mismatch. Mean follow-up was 49 ± 20.26 months. During follow-up, we had no death, and all patients had very good quality of life.

CONCLUSIONS: Aortic valve annulus enlargement can be used with very good early and late results with the final goal to increase the potential benefit of the patient from surgery of aortic valve.

Introduction

Prosthesis - patient mismatch is the common occurrence in aortic valve surgery. Despite the discussions about the impact of this phenomenon on the results of aortic valve surgery, the management of this issue remains one of the major objectives of this type of surgery. One way of solutions for this phenomenon is the use of aortic annulus enlargement technique.

Objectives of this work are to present the early and late results of this technique in our experience.

Patients and Methods

During the period January 2010 - January 2015, 641 patients performed aortic valve surgery isolated or combined with other surgical procedures. We realised aortic annulus enlargement in 10 patients according to Manouguian technique [1] to avoid the occurrence of patient- prosthesis mismatch. The mean age of the group was 49 ± 17.7. There were three males and seven females in all cases; the primary pathology was aortic valve disease. Indications for operation are made according to the European or American associations of Cardiology guidelines [2, 3]. The main diagnostic tool examination

was echocardiography. Six patients were with aortic valve stenosis, two with aortic valve regurgitation and two others with mixed pathology.

Table 1: General data

General Data	
Nr Patients	10
Mean Age	49 ± 17.7
Gender	3M/7F
BSA	1.69 ± 0.14
Pathology	AVS 6 Pt
	AVR 2 Pt
	Mixed 2 Pt
CABG	3 Pt
Mitral	1 Pt
Esc Stand	4.7 ± 1.36
Esc Log	4.35 ± 1.35

The aortic annulus size ranged from 18-23 mm with an average of 20.1 ± average 1.42. The thickness of left ventricle septum and posterior wall were respectively 13.1 ± 0.9 and 12.2 ± 1.24 mm. Body surface of patients ranged from 1.5-2m^2 (mean 1.69 ± 12.14), hospital mortality and perioperative complications (low cardiac debit, pulmonary complications, renal complications, reexploration for bleeding, ventricular arrhythmias, conductions disturbances, wound infections) are considered indicators of early results evaluation.

Table 2: Echocardiographic data

Echocardiografic Data	
EF%	63.3 ± 3.53
Annulus	20.1 ± 1.42
ThPW	12.2 ± 1.24
ThS	13.1 ± 0.9
EDD	52.7 ± 5.7
ESD	30.8 ± 3.2
Mean Grad	54.3 ± 6.4

EF-ejection fraction, ThPW-thickness posterior wall, Ths-the knees septum, EDD-end diastolic diameter, ESD-end systolic diameter, Grd-gradient. BSA-body surface area, Esc stand –Log-euro store standard and logistic.

The mean follow-up time was 49 ± 20.26 months. Survival, clinical condition according to NYHA class and quality of life were indicators of long-term results evaluation. Follow-up was complete. The data were collected from hospital records and periodic clinical and laboratory examinations after hospital discharge. The data are presented in average value and standard deviation (Table 1 and Table 2).

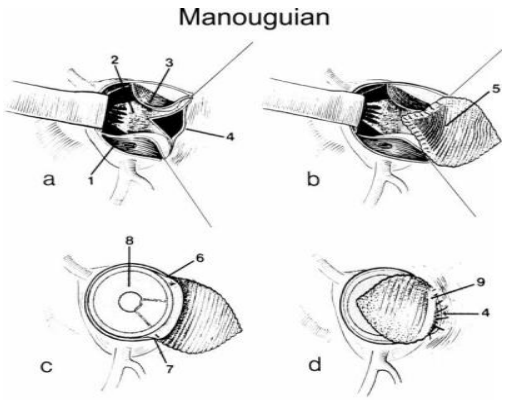
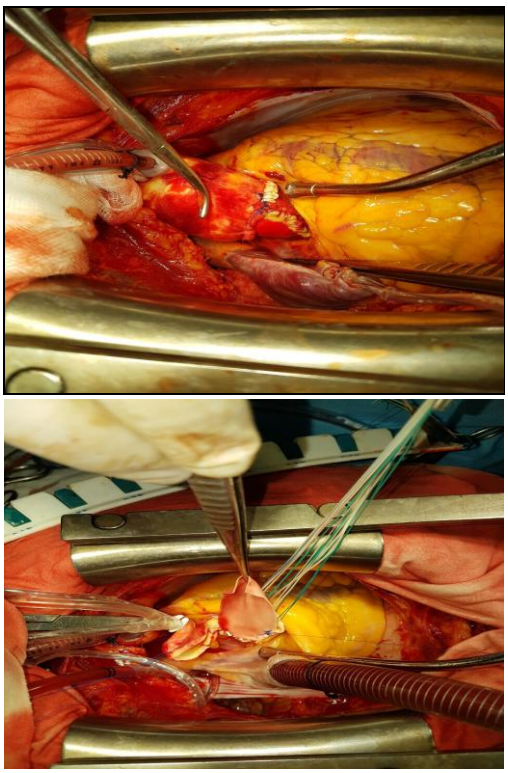


Figure 1: Schematic figure of Manouguian technique

Interventions were performed through the median sternotomy with standard cardiopulmonary bypass and systemic hypothermia to 32^0C. An oblique osteotomy was performed, and myocardial protection was provided by intermittent antegrade crystalloid (first dose), and cold blood cardioplegia delivered directly into the coronary ostium. After excision of the native aortic valve and meticulous decalcification, the aortic annulus was sized. The decision to enlarge the aortic was taken when the 19-mm sizer could not be implanted and according to the body surface area of the patient and the type of prosthesis available. Aortic Annulus enlargement was done using the Manouguian technique. Aortotomy was extended through annulus into the fibrous trigone between the noncoronary cusp and the left coronary cusp to the subaortic curtain and anterior mitral valve leaflet.This defect was closed using a synthetic Teflon patch.



Patch from outside

Patch from inside

Figure 2: Photos during intervention

Results

We had no hospital death in our series. One patient had post-operative pulmonary complications because of his pulmonary preoperative illness. The same patient had low cardiac output and wound infection. All these complications were treated with intensive therapy.

Operative and postoperative data are presented in Table 3. Average prosthesis number used was 20.8 ± 1.75 and ranged from 19-25. The types of the prosthesis implanted were SJM: one SJM Regent, one biological prosthesis SJM Epic Supra and others SJM Standard. The average trans-prosthetic gradient was 16.2 ± 3.44 and ranged from 12-25 mmHg. Indexed effective prosthesis surface mean value was 0.86 ± 0.14 cm^2/m^2. Based on the reference values of effective orifice area we used, no patient come out with severe MPP.

We see that there were long intervention times. This fact can be explained considering that four patients (40 % of the group) have undergone simultaneous surgical procedures (three cases CABG and one case mitral valve repair). Long respiratory assistance and intensive therapy stay time-related to the situation in which one patient (10 % of the group) is treated for a long time in intensive care unit.

Table 3: Operative and postoperative data

Operative and postoperative data	
CPBt	150.3± 19.7
XCt	118.2 ± 15.6
Prot Nr	20.8 ± 1.75
Resp As time	25 ± 21.4
ICU time	102.3 ± 94.7
Hosp time	13.3 ± 7.08
Prot Grad	16.2 ± 3.44
EOAi	0.86 ± 0.14

CPBt = cardiopulmonary bypass time, XCt = cross-clamp time, Prot nr = prothesis number, Resp As time = respiratory assistance time, ICU = intensive care unit, hosp = hospital, Prot grad = prosthesis gradient, EOAi = effective orifice area indexed.

All patients survived during a follow-up period. They were in NYHA 1 clinical status four patients and asymptomatic the other part. The quality of life was very good. One patient had gastrointestinal bleeding from anticoagulation two years after the intervention.

Discussion

Patient-prosthesis mismatch is a common phenomenon in the aortic valve surgery. This problem that has been presented by Rahimtola since 1978 [4] is present also in our series of patients who has performed aortic valve surgery. The incidence resulted from 10.3 % and 67.8 % respectively for severe PPM and moderate PPM [5]. To achieve the maximum of patient benefit from the replacement of the aortic valve, to avoid the phenomenon of patient - prosthesis mismatch, we have followed the strategy of aortic valve annulus enlargement according to Manouguian [1]. The technique is an additional surgical procedure in standard aortic valve, therefore, increases the complexity of the surgery. This is the reason why the discussion about the impact of this procedure in the early and late results of aortic valve surgery is still opened.

Annulus aortic valve enlargement is a safe procedure. In a study where 172 patients have performed aortic annulus enlargement Kulik et al. report mortality 7% while in 540 patients who realised standard aortic valve replacement mortality resulted from 6.5%. Major post-operative complications were no differences between groups with or without annulus enlargement. The PPM incidence and trans-prosthetic gradients were significant lower in the group with AAE ($p < 0.01$, $p < 0.0001$) [6]. Hospital mortality in groups of patients who realised aortic valve replacement with annulus enlargement varies 0.9-7%. Perioperative morbidity has no significant differences compared with standard valve replacement surgery. These results are presented in some separated studies. All studies refer that the occurrence of PPM is always minimised [6-9].

We see that the early results of aortic valve surgery results referred are not influenced by the additional annulus enlargement.This procedure is related strongly to the benefit of diminution of patient – prosthesis mismatch incidence and lower trans-prosthetic gradients. In our group of patients, we had no hospital deaths. The times of intervention, intensive therapy stay and respiratory assistance resulted longer in comparison with a series of our patients with isolated standard aortic valve surgery [5]. These results can be explained by considering the small group of patients (10 patients) among which four patients (40%) have performed simultaneous procedures and one patient who had a preoperative pulmonary disease for which was treated for a long time in intensive therapy unit. No patient was in severe PPM postoperatively.

There are authors by analysing their results refer that small aortic valve prosthesis is not an independent risk factor for the early results and find aortic annulus enlargement among strong predictors of hospital mortality. Aortic annulus enlargement should be used carefully [10].

Urso et al. in a review made regarding the impact of PPM in the early and intermediate the results aortic valve surgery conclude that severe PPM is an independent risk factor for early and intermediate outcomes. This phenomenon should be avoided. Moderate PPM has the impact on patients with severe impairment function of a left ventricle.PPM should be managed because has direct negative impact on early results of aortic valve surgery [11].

Kitamura et al. studied the impact of AAE on long-term results.Ten years survival was 85.7 % in the group that have performed AAE and 62.7 % in the group with small prosthetic but have not realised at the same time AAE. The independence from events related to the prosthesis referred respectively 81% and 58.8%. The difference of survival is not statistically significant, but the difference in absolute value is clear while for events related to the prosthesis is the very important difference [9].

In the contingent of patients named LGAS (low gradient aortic stenosis), PPM should avoid. PPM affects importantly adversely long-term results. In this special group of patients, PPM is related strongly to lower survival and independence from heart failure [12].

In this context in a study where were involved 805 patients and from them 548 patients had VM low function with (EF < 50%) Kulik et al refer that the patients with low EF and with PPM survival and independence from clinical death from heart failure is importantly lower in the long term in comparison with patients without PPM (p = 0.03, p = 0.009) [13].

The last two works take as point reference moderate PPM (SEPi ≤ 0.85 cm^2/m^2). To avoid the negative consequences of MPP in aortic valve surgery results we should include the avoidance strategy of this phenomenon at the time of surgical procedure.

There are studies that denied negative effects of PPM in the early or late results of aortic valve surgery [14, 15], but in a meta-analyses where are selected 34 works and involved 27,186 patients to give response to the question of how long-term results are influenced by PPM realizing AVR was concluded that PPM is associated with increased cardiac or other reasons mortality in long term. The efforts to prevent PPM should be highlighted and disseminated to improve the results of aortic valve surgery [16].

In conclusion, aortic valve annulus enlargement can be used with very good early and late results with the final goal to increase the potential benefit of the patient from surgery of aortic valve.

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Platelet Count in First Trimester of Pregnancy as a Predictor of Perinatal Outcome

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Abstract

AIM: To rule out maternal and pregnancy factors that may contribute to platelet count (PLT) changes in the first trimester of gestation and examine if there is any association between its levels and adverse perinatal outcome.

METHODS: The study population included all patients from the first-trimester visit between 2013-2015 with pregnancy results. Linear multiple regression was constructed to rule out variables that may have a significant contribution to PLT. For each adverse outcome at birth, multiple logistic regression analysis was implemented to estimate the PLT effect.

RESULTS: PLT was measured in 6092 patients. There was the significant contribution on PLT in the first trimester from maternal weight, the presence of rheumatologic disease, BHCG levels and MPV. There was a significant association between PLT and abnormal cardiotocography at delivery (OR 1.004; IC95% 1.001 to 1.007) and C-Section due to abnormal CTG (OR 1.005; IC95% 1.002 to 1.008). When adjusted for factors that interact with PLT there was also a significant association with pH at birth < 7.10 and gestational diabetes.

CONCLUSIONS: Maternal and pregnancy factors can poorly predict relevant changes in PLT at the first trimester of gestation. PLT at first trimester of pregnancy might predict adverse perinatal outcome in combination with other markers.

Introduction

Prediction of perinatal outcome from early stages of pregnancy has become a priority and a line of research in the last decades as a way to improve both maternal and neonatal healthcare. Several methods of screening have been implemented using maternal characteristics and obstetric history, biophysical and biochemical tests under the assumption that this may enhance obstetrical results through pharmacological intervention and a closer follow-up [1, 2].

Normal pregnancy is characterised by an increase in platelet aggregation and a slight decrease in the mean platelet count than in healthy non-pregnant women [3-5]. This can be of no significance or clinical importance and may be due to increased PLT turnover, immune-related mechanisms, plasma dilution, or a complication of a more severe underlying gestational disorder. Moreover, histological examination of the human placenta revealed that during first stages of maternal pregnancy platelets are trapped by endovascular trophoblast aggregates that are formed inside the spiral arteries [6].

Platelets are likely to be activated and release several soluble factors, promoting the invasive capacity of extravillous trophoblasts. Hence, maternal platelets might be a candidate that attracts extravillous trophoblasts into the spiral arteries and encourages maternal vascular remodelling during early placentation process [7].

Mild decreases in platelet count occur in about 3 to 5 % of pregnant women (gestational thrombocytopenia, incidental thrombocytopenia). Gestational thrombocytopenia is characterised by mild asymptomatic low platelet count in a patient without any history of such condition and most frequently during the third trimester. It is not associated with maternal or neonatal sequelae and spontaneously resolves after delivery [8, 9]. Platelet counts are typical > 75,000/μL, with about two-thirds being 130,000 to 150,000/μL.

Longitudinal studies showed that in women with the adverse perinatal outcomes such as Preeclampsia (PE) and intrauterine growth restriction (IUGR) there is a reduction in platelet count and this may predate their development by 3 to 5 weeks [10].

Some others showed that hypertensive disorders cannot be predicted based on platelet count during early stages of pregnancy. Nevertheless, an increased mean platelet volume (MPV) reflects enhanced platelet activation which may be caused by impairment in uteroplacental circulation. When MPV of 10.1 fL or more is used as a threshold, the pregnancies that are destined to develop IUGR and PE can be predicted with considerably high sensitivity and specificity combined with other biochemical markers such as low PAPPA [11,12].

Several reports investigating changes in PLT number, function and MPV indicate increased PLT turnover following activation within the maternal vasculature in impaired placentation conditions such as preeclampsia [13].

The main goal of our research is trying to understand PLT changes in the first trimester of gestation and its relation to pregnancy outcome in an era when sophisticated tests using biochemical or genetic markers are developed. We consider that there might be a place for the simple blood test that can be performed for the identification of women at stake of presenting gestational complications and then be sent to more complex surveillance.

Material and Methods

A retrospective population-based study was performed between 2013 and 2015 to examine whether platelet levels in the first trimester of pregnancy, 8-14 weeks of gestation, are associated with obstetric complications. The second aim is to rule out variables that may have a significant contribution on platelet levels during the first trimester.

Maternal and obstetrical characteristics were collected for patients attending the first-trimester clinic.We assessed the following perinatal outcomes: fetal gender, birth weight, gestational age at birth, bad perinatal outcome defined as: preeclampsia (PE), intrauterine growth retardation as birthweight below the 10^{th} centile (IUGR), perinatal/antenatal death, non-reassuring cardiotocography (CTG), cesarean section (CS) due to non-reassuring CTG, spontaneous delivery before 37 weeks of gestation, Ph at birth < 7.10, newborn resuscitation > 3, Apgar score at 5 min ≤ 7.

Blood samples were obtained by antecubital venepuncture between 8 to 14 weeks of gestation before the clinical visit for routine blood test assessment. Platelet count was measured by an automated hematologic analyser.

Regarding the statistical analysis, values were reported as percentages or means and standard deviations or, for non-normal distributions, as medians and interquartile ranges (IQRs).

Differences of means between two groups were calculated by the Student's *t*-test for independent samples if the normal distribution could be assumed. In the Student's t-test for independent samples, we used the Levene's test for homogeneity of variances. If normality was not valid, we used the nonparametric Mann–Whitney *U*-test. Differences of more than two means between groups were calculated by the ANOVA test if the normal distribution could be assumed or by the nonparametric Kruskal–Wallis test if normality was not valid. The Scheffé test was used for multiple comparisons of means. We firstly performed a simple linear regression with 15 different variables that might have a significant contribution to the platelet count in the first trimester of pregnancy selected by authors criteria. Ten of the above mentioned fifteen variables were used in the multivariate analysis.

The relation between platelets count as the predictor and a bad perinatal outcome was analysed firstly by simple logistic multiple regression. For each adverse outcome at birth, a multiple logistic regression analysis was implemented to estimate the platelets levels effect. All tests were two-tailed. *P*-values below 0.05 were considered statistically significant. Statistical analysis was performed using the SPSS version 18 (SPSS Inc, Chicago, IL, USA).

The present study was approved by the Ethical Committee of Hospital General Universitario Gregorio Marañon de Madrid (Comité ético de Investigacion clínica, reference number OBS05042016, date of approval 05.04.2016).

Results

Platelet count was measured in 6092 patients in the first trimester of pregnancy. The distribution did not follow a normal pattern in our sample (Figure 1); of

these, 22 had thrombocytopenia (0.36%) with PLT below 50,000/µL.

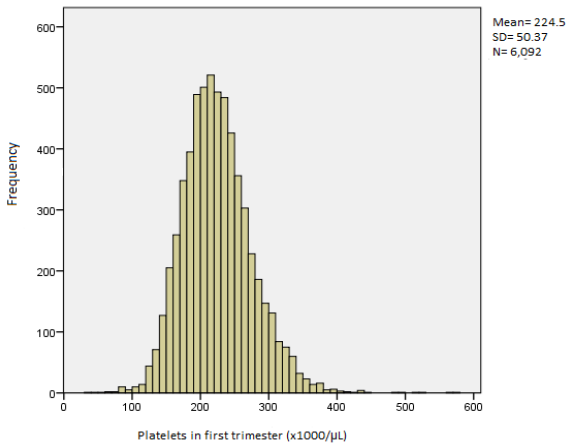

Figure 1: PLT distribution in the first trimester of pregnancy

Predictive linear multivariate regression analysis of platelet count in the first trimester of gestation resulted in a significant model (Table 1, p < 0.001) with an explanatory capacity of 28% (Adjusted R-squared = 0.28).

Table 1: Linear multivariate regression analysis of PLT at first trimester of pregnancy

	Coefficient	95% CI		p-value
		Upper	Lower	
Rheumatological disease Yes/No	-17.941	-26.290	-9.591	<0.001
BHCG (Mom)	-2.208	-4.170	-246	0.027
MPV (fL)	-25.462	-27.015	-23.910	<0.001
Maternal weight (kg)	324	194	454	<0.001

From the total population, 1129 pregnancies (26.8%; IC95% 25.5 to 28.0%) were complicated by any of the following adverse perinatal outcomes as summarised in Table 2. The most frequent ones were abnormal CTG in labour (7.2%; IC95% 6.4 to 7.9%) and IUGR (7.1%; IC95% 6.3 to 7.8%).

Table 2: Perinatal adverse outcomes

	Total (N)	Absolute frequency (n)	(%)	Relative frequency 95% CI	
				lower	upper
Preeclampsia	4223	81	1.9	1.5	2.3
Perinatal/antenatal death	4223	15	0.4	0.2	0.5
Abnormal CTG	4223	302	7.2	6.4	7.9
CS due to abnormal CTG	4223	250	5.9	5.2	6.6
IUGR	4223	298	7.1	6.3	7.8
Preterm birth < 37 sem	4221	125	3.0	2.4	3.5
Ph < 7.10	4220	95	2.3	1.8	2.7
Resuscitation > 3	4222	293	6.9	6.2	7.7
Apgar at 5 min ≤ 7	4221	54	1.3	0.9	1.6
Gestational diabetes	4231	239	5.6	5.0	6.3
Any adverse outcome	4243	1139	26.8	25.5	28.0

According to simple binary logistic regression, there was a significant association between platelets levels in the first trimester (1000/µL) as the predictor and the following adverse outcomes as seen in Table 3.

Table 3: Simple logistic binary regression (predictor PLT 1000//µL)

Adverse perinatal outcome	OR	95% CI		p-value
		lower	Upper	
Preeclampsia	1.002	0.997	1.007	0.470
Perinatal/antenatal death	1.007	0.997	1.017	0.165
Abnormal CTG	1.004	1.001	1.007	0.003
CS due to abnormal CTG	1.005	1.002	1.008	0.001
IUGR	1.000	0.997	1.003	0.918
Preterm birth < 37 sem	1.001	0.997	1.005	0.634
Ph < 7.10	1.000	0.996	1.005	0.963
Resuscitation > 3	1.002	0.999	1.005	0.144
Apgar at 5 min ≤ 7	1.005	0.999	1.010	0.101
Gestational diabetes	1.002	0.999	1.005	0.197
Any adverse outcome	1.002	1.000	1.003	0.040

For each adverse outcome, a multiple logistic binary regression models was constructed and adjusted by rheumatologic disease. BHCG levels, MPV and maternal weight taking into account their interaction with platelets count.

The adjusted effect from PLT resulted into a significant contribution to the following outcomes (Table 4):

Table 4: Estimative model adjusted by interaction factors

Adverse perinatal outcome	OR	95% CI		p-value
		upper	lower	
Preeclampsia	1.002	0.997	1.007	0.470
Perinatal/antenatal death	1.007	0.997	1.017	0.165
Abnormal CTG	$0.988 \times 1.00025^{weight}$	$0.975 \times 1.00004^{weight}$	$1.001 \times 1.00045^{weight}$	0.018
CS due to abnormal CTG	$0.986 \times 1.0003^{weight}$	$0.972 \times 1.0001^{weight}$	$0.999 \times 1.0005^{weight}$	0.007
IUGR	1.000	0.997	1.003	0.918
Preterm birth < 37 sem	1.001	0.997	1.005	0.634
Ph < 7.10	$1.010 \times 0.988^{BHCG}$	$1.002 \times 0.982^{BHCG}$	$1.017 \times 0.994^{BHCG}$	0.009
Resuscitation > 3	1.002	0.999	1.005	0.144
Apgar at 5 min ≤ 7	1.005	0.999	1.010	0.101
Gestational diabetes	$1.007 \times 0.998^{MPV} \times 1.0002^{weight}$	$0.983 \times 0.995^{MPV} \times 1.00004^{weight}$	$1.032 \times 0.99995^{MPV} \times 1.00042^{weight}$	0.019
Any adverse outcome	$0.987 \times 1.0002^{weight}$	$0.978 \times 1.0001^{weight}$	$0.995 \times 1.0004^{weight}$	0.002

Abnormal CTG: The adjusted effect by platelets was significant (p=0.018) and had interaction with maternal weight as seen in this example:

$$0.988 \times 1.00025^{60} = 0.988 \times 1.015 = 1.0029$$

The risk of a non-reassuring CTG was raised by 0.29% for every increase by 1000 platelets/µL in a 60 kg pregnant woman

CS due to abnormal CTG: The adjusted effect by platelets was significant (p=0.007) and had interaction with maternal weight as seen below:

$$0.986 \times 1.0003^{60} = 0.986 \times 1.015 = 1.0009$$

The risk of CS due to abnormal CTG was raised 0.09% for every increase of 1000 platelets/µL in a 60 kg pregnant woman.

Ph < 7.10: The adjusted effect by platelets was significant (p=0.09) and had interaction with BHCG Mom values as seen in the table.

Gestational diabetes: The adjusted effect by platelets was significant (p=0.019) and had interaction with MPV values and maternal weight as seen in this example;

$1.007 \times 0.998^{9} \times 1.0002^{60} = 1.007 \times 0.982 \times 1.012 = 1.0009$

In a 60 kg patient with an MPV of 9 fl in the first trimester, the risk to develop gestational diabetes is raised 0.09% per every increase by 1000 platelets/μL.

Discussion

A relevant finding of our study is that the PLT in the first trimester of pregnancy is not associated with PE. IUGR or preterm delivery. A significant association was found between abnormal CTG. CS due to abnormal CTG. And low pH at birth and gestational diabetes when adjusted for interaction factors and an increase in PLT. This association remains very mild, and its significance could be noticed as a result of a very large sample of patients. We also hypothesised that patients with worse outcome at birth and late stage of pregnancy could show higher PLT values despite the BHCG increment between 8 to 11 weeks as a consequence of an unclear dysregulation in the inflammatory process that occurs during early placentation. However, its clinical importance seems weak further research combining simple markers such as MPV or PAPPA could potentially improve PLT predicting value.

Even though some of the reports did not find an association between low PLT in pregnancy and hypertensive disorders or increase in the perinatal morbidity and mortality. The same show significantly higher rates of preterm birth before 37 weeks of gestation (OR 1.82, 1.1-2.97, 95% CI) were documented among patients with platelets < 100.000/μL [14].

PE and IUGR are thought to be the consequence of impaired placentation due to an inadequate trophoblastic invasion of the spiral arteries. An imbalance between angiogenic and anti-angiogenic proteins [15. 16] and endothelial damage in which platelets may play a role in its pathogenesis [17].

Discordant conclusions have been published regarding platelet number and size variations in normal and complicated pregnancies. Some research groups found no difference in platelet counts and MPV values between complicated and controls, whereas others [18] demonstrated lower platelets and higher MPV in women suffering from PE. However, it seems that early pathogenesis of placental impairment disease during the first weeks of gestation does not have a clear influence on platelet count.

The vascular remodelling that ensures appropriate placental perfusion is an important component of human reproduction and should be secured by several complementary mechanisms. In this respect, promotion of trophoblast invasion by maternal platelets could be one of the multiple mechanisms that regulate this vascular remodelling. Although the vascular changes might occur in the absence of maternal platelets.

The fact that pregnancies with severe platelet defects can achieve an uneventful pregnancy may suggest that maternal platelets are not a fundamental element of human placentation.

The objective of finding a clinically useful first-trimester screening for pregnancy complications is the identification of pregnancies at high-risk of developing gestational and perinatal adverse outcome and through pharmacological intervention and a closer follow-up in this high-risk group reduces the prevalence of the disease or diminishes its deleterious effects [19, 20, 21].

Severe thrombocytopenia with platelet count < 50.000/μL occurs in less than 5 % of preeclamptic women when the disease is established. However, the frequency and severity of thrombocytopenia increase with the severity of PE. and much more increased in patients with HELLP syndrome or those with eclampsia in whom disseminated intravascular coagulation may be a contributing factor [22]. Our research cannot identify or predict patients at risk of developing such problems and presumably not the ones that will have a poorer prognosis once any of these conditions are settled either, but further investigation should question this hypothesis.

The other aim of the study was a method to design a model to predict changes in platelet count in the first trimester by maternal and obstetrical characteristics. Laboratory and ultrasound variables using linear multiple regression shows a mild capacity in explaining platelets variability. Only four variables demonstrated a significant contribution to PLT in the first trimester, but it helped us to understand more precisely what are some of the factors that explicate its variations during early stages of pregnancy

Thrombocytopenia is very common in pregnant women. Evaluation of blood count has shown that thrombocytopenia is the second most common haematological problem in gestation. It may result from diverse aetiologies, but so far a method to predict and quantify platelet count changes at early stages of pregnancy has not been demonstrated.

Platelet count is lower in pregnant compared to healthy non-pregnant women. It is believed that immunological mechanisms at the time of placentation are involved in the process [23]. However, the major factors that change the PLT in pregnancy are still to be specified. Our analysis only included the presence of rheumatologic conditions as the immunological factor, but its contribution resembles weak.

We also know that in pregnancy the demands on the hemostatic and fibrinolytic systems change to

prevent exceeding placental haemorrhage throughout gestation and especially during placental separation at delivery. A relative hypercoagulable state compared with non-pregnant women is caused by the marked increase in coagulation factors, reduced fibrinolysis, and increased platelet activity.

BHCG is secreted by trophoblast. A layer of cells on the outside of the blastocyst that provides the embryo with nutrients and later forms part of the placenta and the fetal membranes. Extravillous cytotrophoblast produces hyperglycosylated hCG (hCG-H). The main form of BHCG present during the first two postconception weeks when implantation is taking place. hCG-H appears to promote invasion of extravillous cytotrophoblast into the myometrium wall to form gripping villi (interstitial invasion) and into the spiral arteries (endovascular invasion) to create a high-flow low-resistance vessels.

During pregnancy, BHCG concentration peaks at 93.598 mIU/mL (range 27.300 to 233.000 mIU/mL) at 8 to 11 weeks of gestation and as seen in our study this hormone is a significant contributor to PLT decrease maybe as a booster of platelet aggregation, activation, placental entrapment and hemodynamic changes (Figure 2).

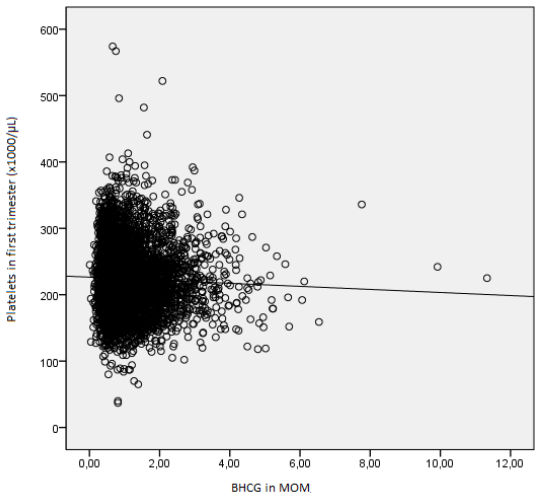

Figure 2: Relation between BHCG in Mom and PLT at first trimester of pregnancy

It has long been known that platelet volume is a direct indicator of increased platelet synthesis and activation [24]. In normal pregnancies, a mild increase in platelet aggregation was observed, which is compensated by increased synthesis and consequently higher MPV values which are consistent with our findings.

Our study has several weaknesses. Despite the large sample size of women with platelet count measurement, only about one-third of them were eligible to take part as observations in our multiple regression works. Many of the variables that we took into account appeared to be irrelevant which necessitated looking for other ones that might be better predictors of platelet count changes in pregnancy.

In conclusion, maternal and pregnancy factors can predict very mildly clinical relevant changes in PLT at the first trimester of gestation. PLT at first trimester of pregnancy might predict adverse perinatal outcome in combination with other markers, but its clinical use remains worthless as a unique test to choose. Further research should be undertaken to test for this purpose.

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Clinical Science

Level of FABP3, FABP4, Nt-proBNP and Total Cardiovascular Risk in the Population of Central Kazakhstan

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Abstract

AIM: The study analyzed the level of cytokines playing the significant role in the diagnosis of circulatory system diseases and total cardiovascular risk.

MATERIAL AND METHODS: The study involved 1,244 residents of Karaganda region. We had studied baseline participant characteristics, in addition to calculating the total cardiovascular risk and assessment of Fatty Acid Binding Proteins 3 (FABP3), Fatty Acid Binding Proteins 4 (FABP4) and N-Terminal Prohormone of Brain Natriuretic Peptide (NT-proBNP) level.

RESULTS: The results showed the combination of high cardiovascular risk (CVR) with increased titers of cardiac markers, reflecting common pathogenic mechanisms in its development, among residents of Karaganda region.

CONCLUSION: The combination of high CVR with the increased titers of cardiac markers showed common pathogenic mechanisms in its development, and support the diagnostic and prognostic value of these parameters among residents of Karaganda region, and also reflects the possibility to include these cardiac markers in the program of screening survey of population for early prevention of cardiovascular disease and its complications.

Introduction

Currently, according to the data of many epidemiological studies cardiovascular disease remains the leading cause of death in our country and abroad [1-7]. Scientists interested the problem of predicting of complications of cardiovascular disease (CVD) for a long time. One of its decisions was the conducting of the large study by the experts of the European Society of Cardiology. Prospective studies with the participation of more than 205 thousand patients were conducted in 12 European countries, including Russia (State Research Center for Preventive Medicine) [8].

The result of this 27-years study was the formation of the European model SCORE (Systemic Coronary Risk Evaluation). Blood cardiac markers found the wide use, reflecting the most of section of pathophysiological process and playing the definite prognostic role, in addition to determining of total cardiovascular risk for early diagnosis of CVD [9-15]. The value of each of the selected cardiac markers studied in detail in the pathogenesis and diagnostics of arterial hypertension, congestive heart failure, atherosclerosis, myocardial infarction and stroke. However, there is insufficient data on the combination of the levels of FABP3, FABP4 and NT-proBNP with a total risk of cardiovascular disease.

The aim of our work was to analyse the role of FABP3, FABP4 and NT-proBNP in the diagnosis of total cardiovascular risk (CVR).

Material and Methods

In addition to determining the levels of FABP3, FABP4 and NT-proBNP, the following work with the population was conducted: survey, anthropometry, blood pressure measurement, determination of blood glucose and total cholesterol. It was conducted the immunological multiplex study of the blood of 1,244 people aged 18-65, including 872 women and 372 men. Pregnant women, people with decompensated cardiac, endocrinology, nephrology pathologies, as well as persons with severe mental illness and oncological diseases were excluded from the study. The index of total cardiovascular risk SCORE was calculated for all examined people [8].

Determination of cardiac markers was carried out by immunofluorescence method using XMap technology on the Bioplex 3D with Human CVD Magnetic Bead Panel 1. We determined the levels of FABP3, NT-proBNP, FABP-4. FABP3 is heart form of protein, binding the fatty acid, and it is detected in patients with acute myocardial infarction, heart failure. It evidences of permanent myocardium damage and is associated with worsening prognosis and high mortality [16, 17]. N-terminal fragment of brain natriuretic peptide (NT-proBNP) is evaluated as a predictor of cardiac events and lethal outcomes in acute and chronic heart failure [18], and also plays a significant role in the formation of atherosclerosis [9, 19]. Increased level of FABP-4, is associated with obesity, insulin resistance, hypertension, atherosclerosis [12, 20-21].

Statistical analysis

For statistical analysis, we used IBM SPSS Statistics, Version 24. Data analysis was performed with the significance level $\alpha = 0.05$. Check on the normal distribution of quantitative data was performed using the Kolmogorov-Smirnov test. Description of the quantitative data was carried out bofy median and quartiles. For qualitative data, it was calculated the proportion of individuals with traits of interest and 95% confidence interval of the proportion calculated by Klopper-Pearson method. We used U criterion of Mann-Whitney to compare the independent samples.

Results

Table 1 and 2 show the baseline characteristics of the examined people depending on gender. The median of age women included in the study was more than median of male (56.00, Q_{25} – 51.00; Q_{75} – 61.00 and 52.00, Q_{25} – 45.00; Q_{75} – 59.00, $p < 0.001$). Assessing the BMI noted that both populations are overweight, and women BMI was significantly greater (29.38, Q_{25} – 25.96; Q_{75} – 33.67 and 27.22, Q_{25} – 24.00; Q_{75} – 30.49, $p < 0.001$).

Table 1: Qualitative baseline participant characteristics

	Men				Women				p-value
	N	Median	Q_{25}	Q_{75}	N	Median	Q_{25}	Q_{75}	
Age, years	372	52.00	45.00	59.00	872	56.00	51.00	61.00	0.000
BMI, kg/m^2	370	27.22	24.00	30.49	867	29.38	25.96	33.67	0.000
Systolic BP, mm Hg	369	130.0	120.0	140.0	869	130.0	120.0	145.0	0.072
Cholesterol, mmol/L	366	4.975	3.870	5.900	866	5.140	3.870	6.120	0.056

The proportion of women with hypertension was much higher than men – 59.08% and 37.20%, respectively ($p < 0.001$), though the median of systolic arterial pressure had no differences. Total cholesterol levels were increased in both groups, but higher rates were observed in women (5.140, Q_{25} – 3.87; Q_{75} – 6.12 and 4.97, Q_{25} – 3.87; Q_{75} – 5.90, $p = 0.005$). Also, the higher percentage of smokers was observed in male population (45.78% and 10.76% respectively, $p < 0.001$).

Table 2: Quantitative baseline participant characteristics

	Men			Women			
	N	%	95% CI	N	%	95% CI	p-value
Arterial hypertension	138	37.20	32.26;42.34	514	59.08	55.73;62.37	0.000
Smoking	168	45.78	40.60;51.03	93	10.76	8.78;13.02	0.000

The results of immunological studies of blood for cardiac markers are described in tables 3-5. The results of the general population (Table 3) show that the median of values of all three cardiac markers was significantly higher in the group of high CVR ($p < 0.05$).

Table 3: Comparison of cardiac markers indicators (pg/ml) in the groups with high and low total cardiovascular risk in the general population

	SCORE, high risk				SCORE, low risk				p-value
	N	Median	Q_{25}	Q_{75}	N	Median	Q_{25}	Q_{75}	
FABP 3	942	2099.06	1449.08	3088.71	302	1686.71	1153.73	2432.48	0.000
NT-proBNP	942	78.63	49.29	109.25	302	67.91	44.25	94.05	0.002
FABP 4	942	15417.30	9148.77	24441.47	302	14587.26	8855.39	20493.94	0.019

Table 4 shows the results of comparing of cardiac markers level in men – only the NT-proBNP level was significantly higher in the group of high CVR (78.49, Q_{25} – 50.58; Q_{75} – 110.28 and 65.91, Q_{25} – 43.99; Q_{75} – 90.10, $p < 0.05$). The differences were not observed in FABP 3 and FABP 4.

Table 4: Comparison of cardiac markers indicators (pg/ml) in the groups with high and low total cardiovascular risk in men

	SCORE, high risk				SCORE, low risk				p-value
	N	Median	Q_{25}	Q_{75}	N	Median	Q_{25}	Q_{75}	
FABP 3	304	1952.23	1396.90	2936.02	68	1676.68	1336.16	2290.45	0.065
NT-proBNP	304	78.49	50.58	110.28	68	65.91	43.99	90.10	0.039
FABP 4	304	14085.63	7711.29	19704.68	68	14685.49	9903.65	21687.69	0.552

In the female population (Table 5), with high probability, the median of titers FABP 3 (2204.09, Q_{25} – 1492.74; Q_{75} – 3277.31 and 1693.39, Q_{25} – 1101.83; Q_{75} – 2442.27, $p < 0.001$), NT-proBNP (78.66, Q_{25} – 49.00; Q_{75} – 108.39 and 68.25, Q_{25} – 44.25; Q_{75} – 98.13, $p < 0.05$) and FABP 4 (16791.89, Q_{25} – 9961.06; Q_{75} – 26256.08 and 14544.90, Q_{25} – 8823.34; Q_{75} – 20112.41, $p < 0.001$) was higher in the group with high total cardiovascular risk.

Table 5: Comparison of cardiac markers (pg/ml) in the groups with high and low total cardiovascular risk in women

	SCORE, high risk				SCORE, low risk				p-value
	N	Median	Q_{25}	Q_{75}	N	Median	Q_{25}	Q_{75}	
FABP 3	638	2204.09	1492.74	3277.31	234	1693.39	1101.83	2442.27	0.000
NT-proBNP	638	78.66	49.00	108.39	234	68.25	44.25	98.13	0.021
FABP 4	638	16791.89	9961.06	26265.08	234	14544.90	8823.34	20112.41	0.000

Discussion

We investigated the level of cardiac form of protein, binding the fatty acids 3 (FABP3), N-terminal prohormone of natriuretic peptide (NT-pro-BNP) and protein, binding fatty acids 4 (FABP 4) in people with low and high total cardiovascular risk. The main results of this study showed that the median of all three cardiac markers was higher in the group with high CVR. Differences were observed only in the male population, where the rate of only one substance (NT-proBNP) had the significantly greater median in the group of persons with high CVR.

We chose FABP3 as one of the cardiac markers localised in cardiac myocytes. It provides the transport of fatty acids, as one of the most important energy resources of heart, to mitochondria. Also, it protects against free radicals accumulated as a result of myocardial ischemia [13, 22-24]. Thus, the higher titers of this protein in the peripheral blood are one of the earliest and specific indicators of myocardial damage of various origins, whether ischemia, cardiomyopathy, heart failure [17, 20, 25-26].

The results of our study showed that in the group women with high total CVR the median of titers of FABP3 significantly higher than in the low-risk group, in a case of the male population it was no differences. This indicates about damaged myocardium in the group with high CVR and reflects the diagnostic and prognostic value of this indicator in patients with cardiovascular disease. This can also be explained by the high number of women in the study and by the results of the comparison of general characteristics, in which more percentage of persons were women with hypertension and the highest median of total cholesterol.

The second cardiac marker, used in this study, was NT-pro-BNP. The peptide is released in response to tension and hypoxia of cardiomyocytes and is used as a diagnostic and prognostic indicator of chronic heart failure, the risk of fatal complications (myocardial infarction, stroke) [18], and also has an effect on the vascular wall, which allows us to estimate the risk of development of atherosclerosis and hypertension [9, 11, 19, 27]. The analysis of the level of titles of NT-pro-BNP shows that the median value in the male and female populations has differences. This may indicate damaged myocardium in the studied group with high CVR and reflects the diagnostic and prognostic value of this indicator in patients with cardiovascular disease.

The last cardiac marker, which was used in the study, was FABP 4. This substance is adipokine, secreted by adipose tissue (adipocytes), and is involved in the regulation of energy metabolism and inflammation process [12]. According to the results of several large studies, the increased titers of this marker associated with obesity, metabolic syndrome, and the risk of developing of the resistance to insulin, diabetes mellitus of type 2 and as a consequence increasing cardiovascular risk [12-14, 22]. In our study, the median titers of the protein are higher in women with high CVR. In the male population, the differences between these values and the level of CVR are not revealed. These results correlate with the presence of large BMI values in the female population.

As a result, the combination of high CVR with the increased titers of cardiac markers showed common pathogenic mechanisms in its development, and support the diagnostic and prognostic value of these parameters among residents of Karaganda region, and also reflects the possibility to include these cardiac markers in the program of screening survey of population for early prevention of cardiovascular disease and its complications.

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Clinical Science

Clinical Spectrum of Cerebral Palsy and Associated Disability in South Egypt: A Local Survey Study

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Abstract

BACKGROUND: Cerebral palsy is the most common cause of motor disability in children with a prevalence of 2-10/1,000 live births in the developing areas.

AIM: The epidemiology, clinical picture, and associated comorbidities in CP have been extensively studied in high-resource countries, but in low-resource areas, including Africa, those studies are still lacking.

METHODS: Cerebral palsy cases were prospectively recruited from every physiotherapy centre in Bani-Mazar city, Egypt, in a cross-sectional study from May 2015 to November 2015.

RESULTS: Two hundred cases were enrolled with a prevalence of 1 per 1000 live births. Within the study population, 72.5% were the spastic type, 16% were dyskinetic, 7% were ataxic, and 4.5% were hypotonic. The most common comorbidities were cognitive impairment and epilepsy affecting 77% and 38%, respectively.

CONCLUSION: Cerebral palsy in developing countries has a higher prevalence and different clinical profile regarding severity and associated disability. The perinatal and high-quality neonatal care together with physical therapy and rehabilitation programs is still lacking in developing countries.

Introduction

Cerebral palsy (CP) is a term that has been formally defined as a group of permanent disorders of the development of movement and posture, causing activity limitation, which is attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy and by secondary musculoskeletal problems [1].

Prevalence estimates range from 1.5-3/1,000 in western countries, with much higher and wider range, 2-10/1,000 live births, in the developing areas [2] Durkin et al. 2016.

In an Egyptian study by El-Tallawy et al., 2014 [3] it was 2.04 per 1000 live births. The variation in prevalence and clinical picture depends mainly on study design, populations, and diagnostic criteria.

The epidemiology, clinical picture, and associated comorbidities in CP have been extensively studied in high-resource countries, but in low-resource areas, including Africa, those studies are still lacking. CP has many risk factors. The most common are low birth weight and perinatal hypoxia accounting for almost 50% and 10-20%, respectively [4].

This study aims at identifying the prevalence and the disability profile and associated comorbidities of CP cases in a prospective cross-sectional study from referral centres of physiotherapy and rehabilitation in Bani-Mazer district, Elminia Governorate, Egypt.

Subjects and Methods

All documented CP cases, according to the consensus definition by Bax et al., 2005 [5], from Bani-Mazar city and related nearby villages have been included in this study which was conducted from May 2015 to November 2015.

Inclusion criteria

The age range was from 3 months to 18 years, with disease onset within the first year of life. Cases were recruited from every physiotherapy and rehabilitation centre.

Exclusion criteria

Cases with developmental regression, malignancy and peripheral central nervous system affection were excluded.

For evaluation

1. The Gross Motor Function Classification System (GMFCS): Is a classification system developed for children with CP. Initially, children with CP were divided into five levels by considering their independency in gross motor functions such as sitting, walking, mobilisation and transfer activities and the tools-equipment.

Motor function is classified based on walking ability. Children classified as GMFCS Levels I or II were categorised as 'walks independently', Level III as 'walks with handheld mobility device', Levels IV as 'limited walking ability', and level V as wheel-chair bound. As motor functions of children differ according to age, functions have been defined as below 2-year old, between 2 and four years old, between 4 and six years old, between 6 and 12 years old, and above 12-year-old for each level**.**

GMFC classification system: LEVEL I - Walks without Limitations, LEVEL II - Walks with Limitations, LEVEL III - Walks Using a Hand-Held Mobility Device, LEVEL IV - Self-Mobility with Limitations; May Use Powered Mobility, LEVEL V - Transported in a Manual Wheelchair.

2. A clinical evaluation carried out including history taking and thorough neurological examination. Associated impairments have been documented by reviewing available formal documents including the history of true recurrent seizures, cognitive assessment, visual acuity, and hearing evaluation. For hearing impairment, an official audiometry result was reviewed.

A formal written consent has been taken from parents or care givers for all cases. The study was approved by the local ethical committee.

Data was analysed using IBM SPSS Statistics 22.

Results

The total population under the age of 18 years old, at the area of study, was 198,776 (32%of total population). The number of CP cases in this population who receive physical therapy services was 200 representing the prevalence of 1 per 1000 live births.

The demographic data of the cases (number = 200) has been presented in Table 1.

Table 1: Demographics of cases (Number = 200)

Variables		Number	%
Gender	Male	110	55
	Female	90	45
Residence	Rural	162	81
	Urbane	38	19
Parents consanguinity	Positive	96	48
	Negative	104	52
Type of delivery	Normal	74	37
	Cesarean	126	63
Gestational age	Pre-term	32	16
	Full-term	163	81.5
	Unknown	5	2.5
Birth weight	Extremely LBW	7	3.5
	Very LBW	10	5
	LBW	36	18
	Normal birth weight	85	42.5
	High birth weight	13	6.5
	Uncertain	49	24.5
Chronological Age	3month < 2year	76	38
	2year < 4year	60	30
	4year < 6year	34	17
	6year < 12year	30	15

LBW = low birth weight

Cases with CP has been divided according to type into spastic (72.5%), dyskinetic (16%), ataxic (7%), and hypotonic (4.5%). Spastic cases have been further categorised according to the distribution of spasticity to diplegic, quadriplegic, and hemiplegic (Table 2).

Table 2: Types of CP and distribution of spasticity

Clinical variables	Number (%)	Total
Sub types of CP		
Spastic	145 (72.5%)	200
Dyskinetic	32 (16%)	
Ataxic	14 (7%)	
Hypotonic	9 (4.5%)	
Distribution of spasticity		
Diplegic	70 (48.27%)	145
Quadriplegic	44 (30.3%)	
Hemiplegic	31 (21.4%)	

CP = cerebral palsy.

Table 3: Motor impairment according to GMFCS

Level Age range	I	II	III	IV	V	Total
0-2y	6	15	22	19	15	76
2-4y	4	20	19	7	8	60
4-6y	6	5	10	7	6	34
6-12y	3	5	15	6	2	30
Total	19	45	66	39	31	200

GMFCS = Gross Motor Classification System.

The distribution of motor impairment according to GMFCS across age groups has been presented in Table 3 and Figure 1.

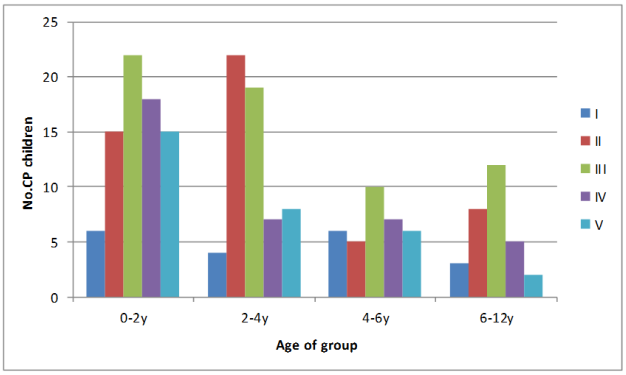

Figure 1: Level of impairment according to Gross Motor Functional Classification system (Birth-12 year)

Cases with hemiplegic type fall mostly in the range from level I through level III on GMFCS scale, while cases with quadriplegia are more disabled on level III through level V. There is a statistically significant difference between spastic subtypes regarding GMFCS score (Table 4).

Table 4: GMFCS according to type of spasticity

GMFCS	Spasticity type				χ^2
	Hemiplegic	Diplegic	Quadriplegic	Total	
I	10	5	0	15	P < 0.001
II	10	23	4	37	
III	10	24	14	48	
IV	1	11	14	26	
V	1	6	12	19	
Total	32	69	44	145	

GMFCS = Gross Motor Classification System.

Associated impairment has been documented using available formal reports. Cognitive impairment was the most common as it affected 77% of cases (Table 5).

Table 5: Associated impairments

Disorder	Number (%)
Cognitive impairment	145 (77%)
Epilepsy	76 (38%)
Visual impairment	9 (4.5 %)
Hearing impairment	5 (2.5 %)

It has been found that both cognitive impairment and epilepsy were found in a higher percentage of children with a higher score on GMFCS (Table 6, 7).

Table 6: Distribution of cases with cognitive impairment according to GMFCS score

		Cognition		Total	P value
		Normal	Affected		
GMFCS	I	11	8 (42.1%)	19	<0.001
	II	18	28 (60.8%)	46	
	III	12	56 (82.3%)	68	
	IV	4	36 (90%)	40	
	V	1	26 (96.2%)	27	
Total		46	154 (77%)	200	

GMFCS = Gross Motor Classification System.

Binary logistic regression models were tested for the relation between GMFCS and both cognitive impairment and epilepsy. It was founded that each grade higher on GMFCS was associated with 2.5 and 1.5 fold increased the risk for occurrence of cognitive impairment and epilepsy, respectively.

Table 7: Distribution of cases with epilepsy according to GMFCS score

		Epilepsy		Total	P value
		Normal	Affected		
GMFCS	I	16	3 (15.7%)	19	0.01
	II	34	12 (26%)	46	
	III	38	30 (44.1%)	68	
	IV	25	15 (37.5%)	40	
	V	11	16 (59.2%)	27	
Total		124	76 (38%)	200	

GMFCS = Gross Motor Classification System.

Discussion

The current study was conducted to establish a data base about children with CP receiving physical therapy services in general or health insurance hospitals as well as private centres in Bani-Mazar district Elminia governorate.

There was a little higher male to female ratio (1.22), almost similar to 1.3 reported by Johnson, 2002 [6] in Europe.

The urban to the rural ratio of cases was 1to 4 which is expected as the antenatal care and the medical services for neonates in general, and those with high-risk factors for CP in particular, are of low calibre and capacity.

According to our sample, there were no cases above 12-year-old receiving physiotherapy service. This finding could be related to the extreme sides of the disability spectrum, being either mild and almost completely rehabilitated, or severe and neglected at home due to logistic issues (difficult transportation of grown-up patients, negative attitude towards severe cases in the low socio-economic population, or financial issues).

The total number of CP cases was 200 cases,

representing 1 per 1000 live birth. Prevalence of CP occurs at a rate of 2-2.5 per 1000 live births in developed countries [5]. Also in Egypt; El-Tallawy [7] reported a prevalence of 2.03and 3.6 per1000 live birth in Al-Kharga District and Al-Quseir city [3], respectively. The lower prevalence can be attributed to multiple factors. First of all, the different methodology as our study includes only those cases under the age of 18 year receiving physiotherapy services. Also, our cases are those with a disability severe enough to push the care givers to seek medical services. Second, the prevalence of CP has dynamic properties related to attitude and quality of health care and neonatal mortality [4].

According to our study, premature delivery and LBW accounted for 16% and 26.5%, respectively. These figures are low in comparison to international figures (78%) reported in developed countries. This difference is expected regarding high mortality rate of premature and LBW and a higher incidence of perinatal hypoxic events [8].

Our results on the types of CP and distribution of spasticity are similar to those reported in developing countries as reported by Kakooza-Mwesige et al. 2015 [9]. Spastic CP is the most common type, worldwide. Similarly, most of our patients (72.5%) were spastic. Dyskinetic CP (16%) is higher than the figures in western countries (6%) [10].

The higher ratio in our area can be explained by the lack of awareness of families to the impact of neonatal hyperbilirubinemia and the reluctance to seek medical advice. The ataxic cases constituted almost 7% of total number which is in consistency with local and international figures [3, 7, 9].

Spastic quadriplegic CP is the most severe form affecting 44 patients (22%) of all CP cases and (30.3%) of spastic CP patients.

Epilepsy and mental sub normality were found in 38% and 77%, respectively. These figures are similar to those reported in Africa [3, 9] but higher than reported in developed areas [10]. The difference can be explained by the greater proportion of cases with extensive bilateral brain injury in diplegic and quadriplegic cases which are more vulnerable to develop symptomatic epilepsy. Also, the definition of mental sub normality in our study was based on available formal IQ test in contrast to the study by El-tallawy et al.,(2014) [3], where the IQ test was available for only 24 cases. It is worth mentioning that epilepsy was related to the level of GMFCS. This finding was also addressed by Hundozi-Hysenaj and Boshnjaku-Dallku, (2008) [11]. Regarding cognitive profile, GMFCS level was a detrimental factor which is consistent with Dalvand et al., (2012) [12], who stated that GMFCS could be considered as a gross proxy for evaluating the cognitive deficit.

The gross motor function severity varied significantly across spastic subtypes (Table 4). GMFCS I through III was found to compress mainly children with diplegia whose gross and fine function is more homogeneous than in children with hemiplegia.

Regarding GMFCS, 9.5% of cases were at level I, 18.5% at level IV, and 15.5% at level V. In the study conducted by Kakooza-Mwesige et al. 2015 [9], the percentage of cases at level I is very similar to little higher percentage at level IV and V. on the other hand, in a Swedish study, 32% of cases were at level I, 15% at level IV, and 16% at level V [13]. The difference mainly lies with level I which is the mildest form. This reflects the effect of public awareness, the different etiologies, the level of neonatal care, the importance of early detection, and the quality of rehabilitation programs.

In conclusion, our study revealed a prevalence of 1 per 1000 live births from the age of 3 months to 18 years. Two-thirds of our study are ambulant, evidence for the paramount importance of early detection and intervention. The most common subtype is spastic CP, while the most common comorbidity is cognitive impairment followed by epilepsy. GMFCS is a useful tool for assessment, and it may offer a good predictor for epilepsy and cognitive impairment. In comparison to international figures, it seems that the perinatal and high-quality neonatal care is still lacking in developing countries. Also, being of a low-resource population, the accessibility to physical therapy and rehabilitation programs is to be revisited.

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Clinical Science

Quality of Life in Patients Following Vertebroplasty

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Abstract

AIM: To examine the quality of life in patients who underwent vertebroplasty treatment and compare it to the preoperative quality of life.

STUDY DESIGN: The Cross-sectional study conducted at the Department of Orthopaedics, Clinical Hospital Centre Osijek.

PATIENTS AND METHODS: The research included 50 patients under stationary treatment in hospital at the Department of Orthopaedics. The research instruments include a questionnaire containing demographic data and the standardised EuroQuol Research Foundation Questionnaire (EQ-5D-5L) consisting of five dimensions which include mobility, self-care, usual activities, pain level and anxiety.

RESULTS: The average score of the current health status before surgery was 67.5 whereas post-operative health was rated 80 ($p < 0.001$). After the procedure, a significantly higher number of respondents reported greater mobility levels, and lower pain intensity; fewer respondents reported feeling anxious or depressed ($p < 0.001$), more respondents rated their self-care abilities higher ($p = 0.003$), and felt improvements when performing usual activities ($p = 0.031$).

CONCLUSION: After the vertebroplasty, a significantly higher number of respondents reported higher levels of mobility, lower pain or discomfort levels, and a smaller number of respondents felt anxious or depressed, more respondents felt they can take better care of themselves, and are better at performing usual activities when compared to the preoperative status.

Introduction

Quality of Life

The World Health Organization (WHO) defines quality of life as individuals' perception of their position in life in the specific cultural, social and environmental context (World Health Organization 1999), while Robert Cummins, the founder of the international group of scientists and researchers "International Well-Being Group", holds a view that the quality of life is a multidimensional construct consisting of: living standard, health, productivity, the possibility of achieving close contacts, security, belonging to a community and a sense of security in the future [1]. Health is one of the factors that affect the personal quality of life, and individual experience perception of the life satisfaction should be recognised as a valuable indicator of the status of the population health. Poor health is undoubtedly one of the external factors that adversely affect the individuals' lives. It affects them not just regarding physical symptoms and thus limiting their functioning, but also causes indirect effects such as changes in the ability to work, potential isolation, increasing dependence on others, bad habits, etc. Two persons can suffer from the same disease, but people differ in their perceptions, attitudes, reactions, hopes, fears [2].

The medical notion of quality of life can be defined as the ability of a person to live after a medical intervention as similar as possible in physical, mental and social terms as he/she did before the surgery or prior illness. In providing health care, a nurse should keep in mind that the quality of life depends on the subjective judgment of an individual, which means that it is individual and cannot be directly linked to the illness a person suffers from [3]. Numerous studies were conducted worldwide on

persons suffering from various physical diseases. Pains are specified as the most important variable, i.e. a physical symptom associated with subjective quality of life.

One of the most common complications of osteoporosis are vertebral compression fractures, which are a common cause of chronic pains, and result in progressive morphological changes of the spine with the development of kyphosis and accompanying additional reduction of body height. These significantly restrict the mobility of patients and deteriorate their overall quality of life. Osteoporotic vertebral compression fractures usually affect the middle and lower spine and thoracolumbar transition and less lumbar segment. In patients with osteoporotic spine, mortality is increased by 23% to 34% compared to patients without fracture [4].

Spine fractures are two to three times more frequent than hip fractures, especially in females. The most recent US data show that at least 700,000 patients per year have the osteoporotic spine fracture, which is one of the leading health problems of the elderly population [5].

Osteoporotic Spine fractures were usually treated conservatively: rest, analgesics, and by application of the Jewett type orthosis or other types of orthoses. Bedrest accelerates the loss of bone mass, and in most patients, these therapy measures do not reduce pain [6].

Surgical treatment of osteoporotic fractures becomes more frequent both in our country and in the world. Modern surgical techniques of treatment are vertebroplasty and kyphoplasty which significantly reduce pain and improve the mobility of patients and thus their quality of life [6].

The goal of this study is to research the quality of life in patients who underwent vertebroplasty compared to the preoperative quality. In this prospective study the data obtained from a questionnaire designed for this study, and from the standardised questionnaire EQ-5D-5L (EuroQol Research Foundation) [7], containing the data on mobility, self-care, usual activities, pain level and anxiety will be analysed.

Patients and Methods

Patients

The subjects were patients with a fractured vertebra under stationary treatment in the Department of Orthopaedics of the University Hospital Center Osijek. The study included 50 patients. The study was conducted from September 2015 to June 2016.

Study Design

Vertebroplasty is a minimally invasive procedure of vertebral reinforcement for treating the painful acute fracture of the vertebral body. While the patient is under local anaesthesia, the surgeon creates a tiny path through a small incision (puncture) in the patient's back to a fractured vertebra, using a needle under x-ray control. Through this channel, bone cement is applied to prevent further collapse. The procedure is performed on one or both sides of the vertebral body. The patient can be verticalized an hour after the procedure, and then he/she can leave the hospital [8].

Health Outcomes

The research instruments include a questionnaire containing demographic data (sex, age, occupation, body height, body weight), questions about location of the vertebral fracture, the cause of the vertebral fracture, duration of difficulties to surgery (in months), date of surgery, satisfaction compared to the preoperative status and whether they would agree to re-surgery in case of another fracture. The standardised EuroQuol Research Foundation Questionnaire (EQ-5D-5L) [7] consisting of dimensions which include five items related to the said dimension was used for self-rating. The first dimension consists of five questions assessing the mobility problems. The second dimension consists of five questions related to personal hygiene (washing) and dressing. The third dimension consists of five questions related to usual activities, e.g. work, study, housework, family or leisure activities). The fourth dimension consists of five questions that determine the level of pain. The fifth domain consists of five questions that determine the level anxiety and depression. At the end of the questionnaire, the patient's health is rated as good or bad. The respondents filled out a questionnaire before and after surgery and after the first check-up, i.e. three weeks after the surgery and the results are expressed by the EQ-5D-5L index.

Statistical Data Processing

Category data are presented in absolute and relative frequencies. Numerical data are described by arithmetic mean and standard deviation when distribution follows normal one, and in other cases by median and limits of the interquartile range. Differences of category variables were tested by the Fisher's exact test. The normality of distribution of numerical variables was tested by the Kolmogorov-Smirnov's test. The differences of normally distributed numerical variables between two dependent groups (before and after surgery) were tested by the Wilcoxon's test. The McNemar's test was used to research depending category variables (before and after surgery). All P values are two-sided. The level of significance was set at $\alpha = 0.05$. The statistical SPSS

software (version 16.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Main Characteristics of Patients

The study was conducted on 50 patients, of whom 11 (22%) males and 39 (78%) females. The median age is 74 years (interquartile range 66-79 years) in the range of 47-90 years. According to work status, 44 (88%) are retirees, 2 (4%) of respondents are housewives or shopmen, and one respondent is an administrative clerk or a hairdresser (2%).

The age median is 74 years (interquartile range 66-79 years). The males are significantly taller (Mann-Whitney U test, $p < 0.001$), who also have higher body weight (Mann-Whitney U test, $p = 0.035$), while there is no significant difference in the body weight index between sexes. The median duration of symptoms is three months (interquartile range of 2 to 5 days (Table 1).

Table 1: Sex-related characteristics of patients

	Median (interquartile range)			p*
	Male	Female	Total	
Age (years)	74 (62 - 80)	73 (67 - 78)	74 (66 - 79)	0.743
Height (cm)	172 (170 - 180)	157 (160 - 165)	163 (158 - 70)	<0.001
Weight (kg)	80 (76 - 90)	72 (62 - 80)	75 (64 - 80)	0.035
BMI (kg/m^2)	26.9 (22.9 - 31.1)	27.9 (24 - 30.5)	27.2 (23.9 - 30.6)	0.656
Duration of difficulties (months)	3 (2 - 6)	3 (2 - 5)	3 (2 - 5)	0.970

*Mann Whitney U test.

According to the fracture localisation, most of the patients, 24 (51.1%) are with the lumbar vertebral fracture, and in 32 (64%) patients the fracture was caused by primary osteoporosis (unknown cause). 47 (91.8%) patients are satisfied with their postoperative status compared to the preoperative status, and 45 (91.8%) reports that they would agree to surgery again in the case of re-fracture (Table 2).

Table 2: Patients according to fracture localisation and cause and satisfaction with surgery

	Number (%) of patients			p*
	Male	Female	Total	
Fracture site (localisation)				
Lumbar vertebra	5 (45.5)	19 (52.8)	24 (51.1)	0.898
Thoracic vertebra	4 (36.4)	12 (33.3)	16 (34)	
Several locations	2 (18.2)	5 (13.9)	7 (14.9)	
Fracture cause				
Primary osteoporosis (unknown cause)	10 (90.9)	22 (56.4)	32 (64)	0.072
Secondary osteoporosis(rheumatoid arthritis, systemic lupus erythematosus)	1 (9.1)	17 (43.6)	18 (36)	
Postoperative satisfaction compared to the previous condition				
Yes	11 (100)	36 (94.7)	47 (95.9)	>0.950
No	0 (0)	2 (5.3)	2 (4.1)	
In a case of re-fracture, would you agree to undergo surgery again?				
Yes	9 (81.8)	36 (94.7)	45 (91.8)	0.214
No	2 (18.2)	2 (5.3)	4 (8.2)	
Total	11 (100)	38 (100)	49 (100)	

*Fisher's exact test.

Quality of Life (EQ-5D-5L)

Twenty-three (46%) respondents reported moderate mobility before surgery compared to 14 (28%) after surgery, and 21 (42%) reported slight problems (Table 3).

Table 3: Pre- and Postoperative Mobility

	Number (%) of patients according to mobility problem					
	No problems	Slight problems	Moderate problems	Severe problems	Unable to walk	Total
Pre-operative	1 (2)	10 (20)	23 (46)	15 (30)	1 (2)	50 (100)
Post operative	12 (24)	21 (42)	14 (28)	3 (6)	0	50 (100)

Nine (18%) respondents reported severe problems at washing or dressing prior to surgery and two respondents after surgery, respectively, whereas 16 (32%) state that they have no problems at washing or dressing (Table 4).

Table 4: Pre- and Postoperative Self-Care

	Number (%) of patients according to self-care problem					
	No problems	Slight problems	Moderate problems	Severe problems	Unable to wash or dress them	Total
Pre-operative	5 (10)	13 (26)	22 (44)	9 (18)	1 (2)	50 (100)
Post operative	16 (32)	21 (42)	11 (22)	2 (4)	0	50 (100)

Thirteen (26 %) respondents have severe problems doing their usual activities before surgery and four respondents (8%) after surgery, respectively, whereas 8 (16%) state that they have no problems doing their usual activities after surgery (Table 5).

Table 5: Pre- and usual postoperative activities

	Number (%) of patients according to the problem related to usual activities					
	No problems	Slight problems	Moderate problems	Severe problems	Unable to do my usual activities	Total
Pre-operative	2 (4)	11 (22)	22 (44)	13 (26)	2 (4)	50 (100)
Post operative	8 (16)	28 (56)	10 (20)	4 (8)	0	50 (100)

Three (6%) respondents do not have pain or discomfort before surgery and 16 (32%) respondents after surgery, respectively (Table 6).

Table 6: Pre- and postoperative pain or discomfort

	Number (%) of patients according to the problem related to pain and discomfort					
	Have no pain or discomfort	Have slight pain or discomfort	Have moderate pain or discomfort	Have severe pain or discomfort	Have extreme pain or discomfort	Total
Pre-operative	3 (6)	13 (26)	19 (38)	14 (28)	1 (2)	50 (100)
Post operative	16 (32)	19 (38)	13 (26)	2 (4)	0	50 (100)

Twelve (24%) respondents report moderate anxiety or depression before surgery, and only 3 (6%) respondents report their moderate anxiety or depression after surgery, whereas only one respondent reported severe anxiety or depression (Table 7).

Table 7: Pre- and postoperative anxiety or depression of respondents

	Number (%) of patients according to the problem related to anxiety and depression					
	Not anxious or depressed slightly anxious or depressed	Slightly anxious or depressed	Moderately anxious or depressed	Severely anxious or depressed extremely anxious or depressed	Extremely anxious or depressed	Total
Pre-operative	15 (30)	16 (32)	12 (24)	7 (14)	0	50 (100)
Post operative	26 (52)	20 (40)	3 (6)	1 (2)	0	50 (100)

Respondents were divided according to whether they have or do not have problems. After surgery, significantly more respondents experience better mobility, feel less pain or discomfort, and fewer respondents are anxious or depressed (McNemar's test, $p < 0.001$), more respondents are more able to do self-care (McNemar's test, $p = 0.003$), and better doing their daily activities (McNemar's test, $p = 0.031$) compared to the preoperative status (Table 8).

Table 8: Division of respondents according to parameters before and after surgery

		Number (%) of patients - preoperative			p*
		Have no problems	Have problems	Total	
Mobility					
Post-operative	Have no problems	1 (100)	11 (22)	12 (24)	<0.001
	Have problems	0	38 (78)	38 (76)	
	Total	1 (100)	49 (100)	50 (100)	
Self-care					
Post-operative	Have no problems	4 (80)	12 (27)	16 (32)	0.003
	Have problems	1 (20)	33 (73)	34 (68)	
	Total	5 (100)	45 (100)	50 (100)	
Usual activity					
Post-operative	Have no problems	2 (100)	6 (13)	8 (16)	0.031
	Have problems	0	42 (87)	42 (84)	
	Total	2 (100)	48 (100)	50 (100)	
Pain and discomfort					
Post operative	Have no problems	3 (100)	13 (28)	16 (32)	<0.001
	Have problems	0	34 (72)	34 (68)	
	Total	3 (100)	47 (100)	50 (100)	
Anxiety and depression					
Post operative	Have no problems	15 (100)	11 (31)	26 (52)	<0.001
	Have problems	0	24 (69)	24 (48)	
	Total	15 (100)	35 (100)	50 (100)	

*McNemar's test.

Mean score of categories and the current health is significantly higher after surgery in all categories (Wilcoxon's test, $p < 0.001$). Mean score of the current health status before surgery was 67.5 (interquartile range from 58.75 to 70) and 80 (interquartile range from 78.75 to 90) after surgery, respectively (Wilcoxon's test, $p < 0.001$) (Table 9).

Table 9: Pre-operative and post-operative self-rated quality of the respondents' life

	Median (interquartile range)		p*
	Pre-operative	Post-operative	
Mobility	3 (3 - 4)	2 (1.75 - 3)	<0.001
Self-care	3 (2 - 3)	2 (1 - 3)	<0.001
Usual activities	3 (2 - 4)	2 (2 - 3)	<0.001
Pain and discomfort	3 (2 - 4)	2 (1 - 3)	<0.001
Anxiety and depression	2 (1 - 3)	1 (1 - 2)	<0.001
Self-rating of health (today)	67.5 (58.75 - 70)	80 (78.75 - 90)	<0.001

*Wilcoxon's test.

Post-operative satisfaction was significantly increased in the case of the lumbar vertebrae fractures, and also in patients with fractures of the thoracic vertebrae. In patients with multiple fracture localisations, the significant difference is found only for mobility (Wilcoxon test, $p = 0.020$) and in the health rating (Wilcoxon test, $p = 0.027$) (Table 10).

Table 10: Pre-operative and post-operative self-rating of quality life of respondents according to the fracture localisation

Fracture localisation	Median (interquartile range)		p*
	Pre-operative	Post-operative	
Lumbar vertebra			
Mobility	3 (3 - 4)	2 (2 - 3)	<0.001
Self-care	3 (2 - 3)	2 (1 - 2)	<0.001
Usual activities	3 (2 - 4)	2 (2 - 2.75)	<0.001
Pain and discomfort	3 (3 - 4)	2 (1 - 3)	<0.001
Anxiety and depression	2 (1.25 - 3.75)	2 (1 - 2)	0.001
Self-rating of health (today)	65 (60 - 70)	82.5 (76.3 - 90)	<0.001
Thoracic vertebra			
Mobility	3 (2.25 - 4)	2 (1.25 - 3)	0.001
Self-care	3 (2 - 3.75)	2 (1.25 - 3)	0.001
Usual activities	3 (3 - 3)	2 (2 - 3)	0.001
Pain and discomfort	2.5 (2 - 3)	2 (1.25 - 2)	0.003
Anxiety and depression	2 (1 - 3)	1 (1 - 2)	0.005
Self-rating of health (today)	70 (56.3 - 73.8)	80 (80 - 90)	<0.001
Several locations			
Mobility	3 (2 - 4)	2 (1 - 3)	0.020
Self-care	3 (1 - 3)	2 (1 - 3)	0.317
Usual activities	4 (1 - 4)	2 (1 - 4)	0.059
Pain and discomfort	3 (2 - 4)	3 (1 - 3)	0.058
Anxiety and depression	2 (1 - 3)	1 (1 - 2)	0.180
Self-rating of health (today)	60 (50 - 80)	70 (55 - 90)	0.027

*Wilcoxon test.

Discussion

The purpose of this study was to research the quality of life in patients who underwent vertebroplasty and compare it to the preoperative quality of life. The study was conducted at the Clinical Hospital Centre Osijek and included 50 patients. The resulting analysis is divided into two parts. The first part of the analysis refers to the main characteristics of respondents, and the second one to the very quality of life that was, for the purpose of this study, evaluated by the standardised EQ-5D-5L Questionnaire (EuroQuol Research Foundation).

The study included participants of both sexes/genders. The results of this research show significantly larger number of females, i.e. 39 (78.0%) compared to the male population. The results of other researchers also indicate the significantly higher share of women in this health problem [9].

The mean age of our patients is 79 years, which is also expected because, according to the literature, the incidence of osteoporosis changes increases with age.

In most respondents, i.e. 24 of them (51.1%) the fracture localisation was at the lumbar vertebra and according to the results obtained 32 respondents (64.0%) stated osteoporosis as the cause of fracture. These results are contrary to the study conducted by

Cvijetić et al., 2007 in Zagreb [10].

According to these authors, the patients aged seventy years more often experience the hip fracture. After the age of 50, the increased incidence of the forearm fractures is noticed, after 60 years of vertebral fractures, and after 70 of hip fractures [10]. These figures may indicate the small sample size.

An interesting and expected fact is that 47 (91.8%) patients are satisfied with their postoperative status compared to the preoperative one, and 45 (91.8%) state that in the case of re-fracture they would again agree to the surgery. It suggests that vertebroplasty is an extremely favourable solution for these patients.

The quality of life before and after vertebroplasty regarding mobility, self- care, doing usual activities, pain and discomfort, anxiety and depression was evaluated by the EQ-5D-5L (EuroQol Research Foundation). This questionnaire is selected because it contains simple and understandable questions to all respondents.

According to the results of our research, the largest number of respondents, i.e., 23 (46.0%) reported pre-operative moderate mobility problems compared to 14 (28.0%) respondents after surgery. This percentage directly points to the high percentage of good quality of performed surgical procedures, because the goals of vertebroplasty are: reducing pain, improving a quality of life, improving biomechanics, reducing the need to use analgesics, preventing further development of deformities [11].

The study also shows that 9 (18.0%) patients have pre-operative problems when washing or dressing compared to 2 patients after surgery, while most of them, i.e. 16 (32.0%) state that they have no problems when washing and dressing. These results are expected and indicate improving the quality of life in patients after the surgery.

Problems in doing their usual activities before surgery have 13 (26.0%) respondents and 4 (8.0%) patients after surgery, respectively. This result also indicates the post-operative improved quality of life. Regarding the difficulty of wearing orthotics, and poor results of conservative treatment, the development of surgical techniques and technology created new possibilities for treatment of the spinal compression fractures. The patient stays in bed for at least an hour, and 24 hours after surgery is discharged from hospital [11].

Only a small number of respondents, i.e. three (6.0%) still feel pain after surgery, while the highest percentage, i.e. 16 respondents (32.0%) state that they do not feel pain after surgery. The results are in agreement with other studies. According to Rapan S et al., reducing pain with vertebroplasty amounts to 75.0 to 90.0% [11].

It is interesting that a large number of respondents, 15 of them (30.0%) were depressed and anxious before surgery while the largest number of respondents, 26 of them (52.0%) does not feel post-operative anxiety and depression. It is expected, as the surgery trauma is minimised, the stability is provided immediately as well as rapid recovery of patients after surgery. Surgical patients are exposed to stronger anxiety, fear and depression than other patients because of exposure to the inevitability of surgical intervention, that is additionally aggravated by the fear of pain, anaesthesia, injury and, ultimately, death. The psychological preparation of patients includes informing patients about the procedure (duration, the order of actions, an expected level of discomfort or pain, etc.), modelling (usually watching short movie clips), learning coping strategies and providing emotional support [12]. Pre-operative preparation, provides better subjective enduring the surgery procedure and the postoperative course of a disease, reducing the need for intensive engagement of health professionals in post-operative treatment. This, in fact, reduces the number of days which patients spend in the hospital, which reduces the cost of treatment [12].

When preparing a patient for surgery, it is extremely important to inform him/her about the procedure, including information about common stress reactions and ways of their mitigation and learning how to control their stress reactions. This procedure is aimed to reduce the number of stresses that the patient will experience and strengthen the individual so as not to experience more serious consequences of a large sudden stress. The most effective information is those which contain information about what the patient will experience during the procedure (see, hear, feel) and details about the chronological course of the procedure. Accordingly, the patient will develop realistic, practical, unemotional expectations, which provide him/her with better-coping strategies [10].

After surgery, significantly more respondents experience better mobility, feel less pain or discomfort, and fewer respondents are anxious or depressed, more patients can take better self-care, and doing everyday activities better than before surgery. This confirms the hypothesis of our research. The pain level and the need to take painkillers are reduced immediately; owing to quick mobility they can self-care and doing their daily activities, thereby also increasing the level of quality of life. The results of vertebroplasty published so far are highly positive [11].

The mean scores of the current health of our respondents are significantly higher after surgery in all categories ($p < 0.001$). It is understandable because patients get earlier out of bed, pain score is lower, or there is no pain at all, they go home on the same or the next day to their familiar social environment that also helps their faster psychological recovery. With

about 15% of a filled-up vertebral body with cement, a satisfactory strength of a fractured vertebra is achieved.

The mean score of the current health before surgery in our patients is 67.5, and the mean score following surgery is 80. This study using the EQ-5D-5L (EuroQol Research Foundation) questionnaire has its limitations. The study involved a relatively small number of patients operated in one health facility.

Statistically, significant difference exists in self-rating of a quality of life of our patients according to fracture localisation that shows us increased satisfaction with the quality of life after surgery at the lumbar vertebrae fracture as well as at the thoracic vertebral fracture. Such results are expected. The operative trauma is minimal, the current stability and rapid mobilisation of the patient are provided, which, by application of the new safer generation of highly viscosity cement, makes it the method of choice in the treatment of the compression fractures of vertebral body [11].

In patients with fractures at several locations, the only difference occurs in the self-rated quality of life of mobility and the health assessment made at the first post-operative check-up. Two or more fractures because of reduced lung capacity, reduce mobility, cause chronic pain, loss of appetite and depressive syndromes. As mentioned above, in all subjects including patients who have multiple fracture locations the quality of life is significantly improved simultaneously reducing difficulties in walk and mobility after surgery.

By the defined goal, the following can be concluded from this research:

The level of quality of life in patients that underwent treatment with vertebroplasty is significantly improved compared to the pre-operative level.

After surgery, significantly more respondents experience better mobility, feel less pain or discomfort, and fewer respondents are anxious or depressed, more patients can take better self-care, and doing everyday activities compared to the preoperative status.

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Personality Characteristics as Predictive Factors for the Occurrence of Depressive Disorder

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Abstract

BACKGROUND: The depressive disorder is one of the most frequent mental disorders, which is often associated with severe dysfunctionality. Personality traits are considered as important factors for the occurrence of depressive disorder.

AIM: To determine the specificity of personality dimensions as predictive factors of depressive disorder.

METHODS: This research was conducted at the University Psychiatric Clinic Skopje as a "case-control" study. TCI-R (temperament and character inventory – revised) was used as the main research instrument.

RESULTS: There are specific personality traits expressed through high scores of Harm Avoidance and low scores of Self –Directedness traits as predictive factors related to an incidence of the depressive disorder.

CONCLUSION: The results of this study show that certain personal traits, and more specific HA and SD, are with a specific predictability of the depressive disorder.

Introduction

Cloninger has developed personality theory as the biopsychosocial model of temperament and character, which is based on biological, neurophysiological, psychological and genetic studies [1-3]. It describes the relationship between personality biogenetic structure and mental disorders. Cloninger proposed that person can be considered as a multidimensional construct that includes lower and higher levels of personal functioning through the features of temperament and character. Cloninger conceptualises personality as the combination of two interrelated domains: temperament and character traits.

Temperament is reflecting heritable and neurobiologically based differences in behavioural conditioning, and character traits reflecting both neurobiological and sociocultural mechanisms of semantic and self-aware learning. Those domains are hypothesised to interact as a nonlinear dynamic system regulating the development of human psychological functions [4, 5].

Personality system was proposed as the seven-factor model of temperament and character. Cloninger et all. proposed that temperament consists of four heritable dimensions: Novelty-Seeking (NS); Harm-Avoidance (HA); and Reward Dependence (RD), from which the fourth dimension Persistence (P) emerged.

Cloninger hypothesised that temperament traits are determined genetically and correlated with dopaminergic, serotonergic and noradrenergic activities, with early life manifestation. It is discussed that they have strong relations with the older cortico-

striatal and limbic systems that regulate habits and skills.

Temperament is largely genetically determined and configures automatic behavioural responses, which are related to vulnerability to a wide range of mental disorders. Cloninger et all., proposed three dimensions of character which mature in adulthood, using them to measure a person's humanistic and transpersonal style: Self-Directedness (SD), Cooperativeness (C), and Self-Transcendence (ST).

These character dimensions present persons mental self-government and can measure the presence of personality disorder. Cloninger et all. have hypothesised that character dimensions are influenced environmentally. However, some authors have suggested that they are related with recently evolved regions of the brain - such as the frontal, temporal, and parietal neocortex - that regulate learning of facts and propositions. However, Cloninger has later acknowledged that the relationship between neurotransmitters and temperament is more complex than the originally postulated [4].

Temperament traits

Novelty was seeking: Novelty seeking (NS) is explained as the tendency toward exploratory activity and intense excitement in response to novel stimuli, linked with low basal dopaminergic activity.

Harm avoidance: Harm avoidance (HA) is explained as a tendency to respond intensely to aversive stimuli and to avoid punishment, linked with high serotonergic activity.

Reward dependence: Reward dependence (RD), is explained as the tendency to respond intensely to that was originally hypothesised to be linked with low basal noradrenergic activity.

Persistence: Persistence (P) is the dimension of personality temperament, which indicates person's perseverance in their intentions and actions, despite relative chances of success.

Character traits

Self –Directedness: Self –Directedness (SD) refers to the person the ability to adjust behaviour according to the selected goals and values. It is the source of a sense of personal integrity and self-esteem.

Cooperatives: Cooperativeness (C) is defined as the ability of the person to accept and identify with other people.

Self – Transcendence: Self-Transcendence refers to the interest people have in searching for something elevated, something beyond their individual existence [23]. According to Cloninger's model, self-transcendence can manifest as an intuitive understanding of elevated aspects of humanity, like compassion, ethics, art, and culture.

Relation of temperament and character traits with the emergence of depressive disorder

The relationship between affective disorders and personality is complex. Personality features may predispose an individual to, result from, or modify clinical symptoms of a depressive illness, or be an attenuated expression of a Self –Directedness n affective disorder [6]. Several clinical studies indicate that personality traits can be used to predict further vulnerability to mood disorders [7-10].

Cloninger's Personality model is quite adequate for clinical use as in the process of assessing the risk of a depressive disorder and in the planning of appropriate antidepressant treatment. Cloninger suggests that the interaction of all dimensions of personality may influence vulnerability to depression [11]. Relevant scientific studies prove the clinical use of Cloninger's theory, especially in patients with the unipolar depressive disorder. These studies demonstrate that high-HA in relation with other personal characteristics, among other is associated with the onset of a depressive disorder, and familial vulnerability to unipolar depression is associated mostly with high HA and low SD [12-15].

In recent years TCI is widely used for determination of the personal characteristic of people with depression. Result in many studies show higher levels of HA and ST and a lower level of SD and C, in comparison with the control groups [11, 17-20]. Studies indicate that several clinical features specific to hit the highway connect such as recurrence of mood changes, and comorbidity with other psychiatric conditions associated with personality characteristics. The presence of comorbid anxiety disorders is most frequent, compared to control groups [13].

In line with the most research in this field, the results show that as the most effective dimensions of personality with the distinctive predictability of occurrence of depressive disorder can serve HA and SD dimensions of personality. Depressed patients exhibit higher harm avoidance scores as well as lower self-directedness scores as compared to healthy controls in most of the studies, as well as in this study. Regarding other traits, results differ, and there are different types of analysis. Some authors are finding lower C and higher ST and RD, but with conclusions that these scores are likely to state dependent. Svrakic has concluded that high scores of SD and C are more common in people with mood disorders [21]. Rosenström et all has reported that characteristic of people with major depressive disorder (MDD) are

dependable of mood state [22]. Hi LU has concluded that trait depression and anxiety were linked to high harm avoidance and low self-directedness, and trait depression was linked to high self-transcendence [23]. Other studies have shown that antidepressants are changing personality characteristics after successful therapy outcome, and some studies even showed that temperament might influence response rate to antidepressant treatments in patients with major depression [24].

The main purpose of this study is to determine the role of specific personality traits as predictors of depressive disorder.

Methods

Research tools

Two questionnaires were used as research tools.

For depression measurement: The Beck Depression Inventory is a 21-question multiple-choice self-report inventory. It is widely used the questionnaire to assess the presence and severity of depressive symptoms. They assessed four points scale of 0 to 3, based on the weight of each question. Beck (1996) classifies the total score as follows: 0 -9 normal range; 10-18 minimal depressive symptoms; 19-28 moderate symptoms and severe symptoms 29-63 [25, 26].

For personality measurement: Cloninger's Temperament and Character Inventory-Revised (TCI-R) is 240 items self-report questionnaire with 5-grade Likert scale responses ranging from definitely false to true. It is intended to assess the individual differences of the four temperaments (Harm Avoidance, Novelty Seeking, Reward Dependence and Persistence) and three character higher-order dimensions (Self-Directedness, Cooperativeness and Self-Transcendence). Each higher order dimension if further divided into sub-scales. TCI has been proven internally consistent and factor-analytically valid tool for clinical and legal samples [27-31].

Data was analysed using SPSS version 17. One way ANOVA was used to compare the mean score results between the groups, with the level of significance set at 5%.

Subject and procedures

Examined group (EG): A set of questionnaires was twice applied to the participants of the examined group – inpatients in the University Clinic of Psychiatry Skopje, diagnosed with the recurrent depressive disorder (F33.x). A total of 20 subjects were included in this study, ten males (50%), and ten women (50%).

Their mean age was 35.9 years, SD $\pm$ 6.8 years. First time (T1), questionnaires were applied during the depressive episode, and a second time (T2) after three months anti-depressive treatment (89 days $\pm$ 13.5 days).

Control Group (CG): 20 individuals – volunteers, without the history of mental illnesses or relatives with mental illnesses. The research tools were applied once (T1 time), ten males (50%), and ten women (50%). Their mean age was 32.7 years, SD $\pm$ 4.9 years.

Informed consent was signed by all participants form both groups. This research was conducted at the University Psychiatric Clinic - Skopje.

Results

The obtained results show that there are significantly relevant differences of certain personality traits between the both groups of respondents, indicating that HA high scores and SD low scores are characteristic of people with a depressive disorder, and therefore predictors for its occurrence (Table 1).

Table 1: Comparison of personality traits between depress patients and controls

		Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum	p
				Lower Bound	Upper Bound			
NS_TOTAL	EG before treatment	94.40	5.67	91.22	96.77	79	104	.004
	EG after treatment	102.33	6.33	96.79	107.77	83	114	
	CG	104.70	6.95	93.82	109.88	83	113	
HA_TOTAL	EG before treatment	113.44	9.98	106.75	119.04	95	159	<0.01
	EG after treatment	107.30	8.47	104.52	108.08	84	130	
	CG	94.49	8.99	90.01	100.01	88	120	
RD_TOTAL	EG before treatment	99.14	6.10	96.17	102.44	88	120	.048
	EG after treatment	103.97	6.52	100.42	105.53	93	120	
	CG	105.97	6.06	104.35	107.51	93	120	
P_TOTAL	EG before treatment	114.99	10.46	112.31	117.76	88	150	.026
	EG after treatment	116.83	10.64	114.29	119.37	93	162	
	CG	117.18	10.15	115.50	120.93	94	155	
SD_TOTAL	EG before treatment	122.34	5.44	118.93	125.72	106	139	<0.01
	EG after treatment	127.67	6.56	121.96	133.13	110	137	
	CG	142.43	7.60	133.07	155.14	124	159	
C_TOTAL	EG before treatment	115.80	5.35	110.93	118.72	102	129	0.045.
	EG after treatment	118.55	6.56	113.96	123.13	104	141	
	CG	125.88	7.60	119.07	128.14	109	148	
ST_TOTAL	EG before treatment	72.84	5.35	70.93	73.72	59	86	0.23
	EG after treatment	71.89	6.56	69.96	73.13	48	85	
	CG	71.32	7.60	71.07	75.14	49	87	

Discussion

Our findings show that the human personality consists of multiple dimensions that interact as a complex adaptive system, not as a set of individual components. The results, which are in line with most studies in this field, are conclusive that certain personality characteristics could be assessed as predictors of depressive disorder. Scores of dimensions Harm Avoidance (HA) and Self – Directedness (SD) presented significant differences in scores between EG and CG, which do not change significantly even after treatment, suggesting that these characteristic values for people with depression.

This study has defined high scores of HA and low scores of SD as predictors of the occurrence of depressive disorder. Namely, after antidepressant treatment, scores of HA and SD remain close to values before treatment, which means that high HA and low SD are typical for people who suffer from a depressive disorder. The results of TCI inventory indicated that HA is an emotional marker for vulnerability to depressive disorder and SD represents the marker for executive functions for protection. These conclusions are in line with findings of many scientific types of research; confirming that high scores of HA and low scores of SD are significant predictors of vulnerability to depressive disorder [15].

Harm Avoidance (HA) is a characteristic of a person who is associated with inhibition or interruption of a certain kind of behaviour in any frustrated situation. Persons who have high scores of HA are characterised d by uncertainty, light tiredness, seclusion, pessimism, and is described as fearful, inhibited, with the constant anticipation of damage, while a person with low scores is described as calm, uninhibited, carefree, energetic, and optimist [2].

Taking into account the total values of HA for all groups, it can be concluded that people with high levels of HA are at increased risk of depressive disorder, or are characteristic of a population that already had depressive episodes. With high levels of the personality, characteristic HA can be described tendency toward negative emotions such as fear, shyness and constant concern. These personality traits are characteristic of a person with a higher risk of the depressive disorder. These values are accepted as a general characteristic of people with the depressive disorder. However, the mood state of the depressive patient should be taken into consideration because of possible bias. The results of relevant studies suggest that elevated HA are due to personality characteristics, and are characteristic of people prone to depression.

The obtained results are also leading to conclusions that low levels of SD can be a risk factor for depression; however is not clear how low SD can cause depression. SD as a feature of personality involves the ability of individuals to control their behaviour, with the high capacity for adaptability to new requirements or conditions, reinforcing behavioural patterns aimed at satisfying individual targets and selected values [2-3].

Persons who have high scores for SD are characterised by responsibility, maturity, self-respect, initiative, determination for achievement, with a high degree of insight. On the other hand, people who have low scores for SD are characterised by a sense of inferiority, lack of initiative, proneness to wishful thinking, blaming others for their mistakes. These characteristics are very similar to the description of the depressive person, so it is presumable that low SD scores are linked occurrence of depression. Such findings are stressing conclusions that those subjects with high SD are more able to cope effectively and successfully with difficult life situations or to adapt accordingly and to use their defence mechanisms to deal with the stressor situation [18, 32-34].

Some of the others dimensions are also influenced by depressive episode, but the conclusion is that they are variably influenced by mood state and that they don't have characteristics of prediction.

Novelty seeking (NS) is associated with the initiation of interest for new events or things, and of the appropriate action. NS median values after treatment of the depressive patients are closer to the values of the control group [35]. This indicates that this personality characteristic is probably changeable as a result of a depressive disorder and that due to the process of recovery values are closer to those of the control group. This aspect, along with the results of the correlation of the total value of NA (negative correlation with Beck scale) indicates that this personality characteristic can be an indicator of the success of antidepressant treatment rather than a predictor of depression.

Reward dependence (RD) is characterised by a tendency toward dependence on signals of reward, especially verbal signals of social approval, social support and present mood state. As the results of other relevant research, results of our study show that the values of RD are correlated with depressive mood [36]. A change in scores of RD reflects the present mood state, and it can be assumed that the various expressions of depressive symptoms showed different influence on personality characteristics. RD is negatively correlated with Beck scale, which shows that reducing the Beck scale scores is correlated with an increase of RD scores.

Cooperation (C) is the dimension of the character which is defined as the ability of a person identification and acceptance by others [11]. The results obtained from personality dimension C, during can be concluded that its score is dependable of mood state, and average values after antidepressant treatment are closed to control group. This result is leading to the conclusion that C is not having the predictability of occurrence of depression.

Results obtained have shown that some of the personality characteristics are not influenced by mood state: Persistence (P) is the personality temperament dimension, which indicates whether person's perseverance is in their intentions and actions and despite the relative chances of success [38]. The results obtained in this study show that P does not qualify as any of predictability of occurrence of depressive disorder nor the success of antidepressant therapy. Certain changes are interpreted as variables dependent on the current affective state, i.e. changes in scores with a certain value in a depressed state and after the treatment.

Self-transcendence (ST) is the dimension of the character that relates to the spiritual aspects of the person. The differences in the values of self-overcoming feature did not show statistically significant difference [11]. Obtained results are not leading to the conclusion that this personality characteristic lacks specificity for any predictability of occurrence, nor are dependable of the mood state, i.e. the antidepressant treatment is without influence on this particular personality characteristic.

However, beside general conclusions which indicate that HA and SD may be a relevant predictors of the occurrence of depressive disorder, this kind of interpretation or conclusion can not be generalised. Namely, a very important circumstance is referred to the relationship with other personal dimensions. Many authors suggest interplay with other features of personality such as NS, RD or ST, can be of more important influence than singular dimension itself.

In conclusion, the results of this study show that certain personal traits, and more specific HA and SD, are with a specific predictability of the depressive disorder. Personality dimensions HA and SD differ significantly among the individuals from the examined and control group, which gives it a feature of risk factors for the emergence of the depressive disorder. Although these results are correlated with other scientific researches, it is important to mention that there is a discussion whether they are the result of the primary personal characteristics, or are the result of a personality change due to recurrent depressive disorder. These features should be considered independently, but should always acknowledge the interaction and mutual influence with other personality characteristics. So far in psychiatric science reliable indicators are not established, that would indicate the possibility to predict relapse of depressive episodes. However, these findings could lead to a development of an individual approach in the treatment of the depressive disorder [11, 38, 39].

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Clinical Science

Tumour Necrosis Factor-A, Interleukin-1 and Interleukin-6 Serum Levels and Its Correlation with Pain Severity in Chronic Tension-Type Headache Patients: Analysing Effect of Dexketoprofen Administration

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Abstract

AIM: The purpose of this study is to see the effect of Dexketoprofen on TNF-α, IL-1, and IL-6 serum levels in Chronic Tension-Type Headache (CTTH) patients and its correlation with pain severity.

METHOD: The study subjects were recruited consecutively from the study population. Venous blood was taken at baseline to measure serum levels of TNF-α, IL-1, and IL-6 and after ten consecutive days of Dexketoprofen 25 mg once daily.

RESULTS: Twenty three subjects participated in this study, 3 male (13.0%) and 20 female (87%). A significant difference between NRS score at baseline and after treatment (4.86 ± 1.82 vs. 1.96 ± 1.40, p = 0.001) was found. No significant difference found between baseline and after treatment TNF-α (1.48 ± 0.65 pg/dl vs. 1.48 ± 0.63 pg/dl, p = 0.963), IL-1 (0.16 ± 0.80 pg/dl vs. 0.26 ± 0.31 pg/dl, p = 0.168) nor IL-6 serum levels (1.06 ± 0.83 pg/dl vs. 1.04 ± 0.81 pg/dl, p = 0.915). A weak negative (R = -0.266) non significant correlation (p = 0.219) was found between NRS score and TNF-α. A positive weak negative (R = 0.221) non significant correlation (p = 0.311) between NRS score and IL-1. NRS score and IL-6 had a negative very weak (R = -0.019) non significant negative correlation (p = 0.931).

CONCLUSIONS: Dexketoprofen decreased pain intensity significantly (p = 0.001), but had no effect on TNF-α IL-1 nor IL-6 serum levels. NRS score had a weak and non significant negative correlation with TNF-α, a weak and non significant positive correlation with IL-1, and a very weak and non significant negative correlation with IL-6 serum levels.

Introduction

A tension-type headache (TTH) is the most common form of a primary headache. Chronic tension-type headache (CTTH) differs from the episodic forms not only in frequency but also on pathophysiology, lack of effect of most treatment strategies, more medication overuse, more disability, and higher personal and socioeconomic costs [1]. Globally, the percentages of the adult population with an active headache disorder are 46a % headache in general, 11a % migraine, 42% TTH and 3% chronic daily headache [2].

In the past, several studies have measured the levels of cytokines in the blood of headache patients, mostly migraine. Bo *et al.,* studied the level of cytokines in cerebrospinal fluid (CSF) in headache patients and found elevated levels of IL-1, TGF-b1 (*transforming growth factor-b1*), and MCP-1 (*monocyte chemoattractant protein-1*) in episodic tension-type headache (ETTH) and migraine compared to controls, and there were significant differences in MCP-1 between carcinogenic headache and migraine without aura [3]. Kocer found an increasing level of IL-6 in patients with ETTH and CTTH compared to controls. Therefore, they believe that IL-6 is involved in the induction of pain or inflammatory mechanisms in TTH [4]. One study by Backonja also found elevated receptor levels of TNF

in CSF and blood, elevated levels of IL-1β in CSF that was associated with pain intensity, whereas IL-10 was inversely correlated with pain symptoms [5]. Serum levels of IL-1β were significantly elevated in CTTH patients compare to healthy controls, while IL-18 levels were significantly elevated in men with CTTH, in a study by Vedova *et.al* [6].

Dexketoprofen Trometamol, a COX-inhibitor is administered orally with max 0.25-0.75 hours. Dexketoprofen is superior to placebo in relieving moderate to severe pain. Dose-response relationship between 12.5 mg and 25 mg can be seen as a time-effect curve, where the superiority of Dexketoprofen 25 mg is more likely due to the duration of action expansion more than increasing dosage. The medicine is also well tolerated [7].

Prior studies have found a positive relationship between the numbers of cytokines with some types of a headache. Unfortunately, most measurements of cytokine levels were performed in the CSF make it relatively difficult for routine examination in daily practice. The purpose of this study is to measure the serum levels of TNF-α, IL-1, IL-6 in CTTH patients before and after given Dexketoprofen and its correlation with pain severity.

Material and Methods

This research was done at the Adam Malik Hospital and Bukit Barisan Army Hospital Medan, Indonesia from January 2013 - June 2014 and approved by the Ethics Committee for Health Research School of Medicine in University of Sumatera Utara. The subjects were recruited consecutively from the study population. Diagnosis of CTTH was made based on the diagnostic criteria as stated in the ICH-X. NRS score was taken from all subjects at baseline as well as blood for TNF-α, IL-1 and IL-6 serum level measurement. Each subject was given Dexketoprofen 25 mg once daily for ten consecutive days. The day after the last dosage, all subjects were asked to score their pain severity at that time by using NRS. The second blood samples were taken for the second TNF-α, IL-1 and IL-6 serum level measurement. T-paired test with the level of significance $p < 0.5$ was performed to analyse differences between NRS score, TNF-α, IL-1 and IL-6 serum before and after Dexketoprofen administration.

Results

Data from 23 subjects who followed the whole procedure were analysed further. Twenty-three CTTH patients participated in this study, three subjects were men (13.0%), and 20 subjects were women (87%). There was a significant difference ($p = 0.001$) between baseline NRS score (4.86 ± 1.82) with NRS score after Dexketoprofen administration (1.96 ± 1.40). No significant difference ($p = 0.963$) was found between baseline TNF-α (1.48 ± 0.65 pg/dl) with TNF-α level after treatment (1.48 ± 0.63 pg/dl). There is also no significant difference was found between baseline and after 10-day Dexketoprofen administration for IL-1 serum (0.16 ± 0.80 pg/dl vs 0.26 ± 0.31 pg/dl, $p = 0.168$) and IL-6 serum (1.06 ± 0.83 pg/dl vs 1.04 ± 0.81 pg/dl, $p = 0.687$) (Table 1).

Table 1: NRS score, TNF-α, IL-1 and IL-6 serum level before and after Dexketoprofen administration

Variable	Dexketoprofen		*p* *
	Before (n ; x ± SD)	After (n ; x ± SD)	
NRS	23 ; 4,86 ± 1,82	23 ; 1,96 ± 1,40	0,001 **
TNF-α	23 ; 1,48 ± 0,65	23 ; 1,48 ± 0,63	0,963
IL-1	23 ; 0,16 ± 0,80	23 ; 0,26 ± 0,31	0,168
IL-6	23 ; 1,06 ± 0,83	23 ; 1,04 ± 0,81	0,915

After Dexketoprofen administration, the NRS score showed a weak negative and non-significant correlation with the serum level of TNF- α ($R = -0.266$; $p = 0.219$). NRS score has a weak positive non significant correlation with IL-1 serum level ($R = 0.221$; $p = 0.311$), and a very weak negative and non significant correlation with IL-6 ($R = -0.019$; $p = 0.931$) (Table 2).

Table 2: Correlation between NRS score and TNF-α, kadar IL-1 and kadar IL-6 serum level after Dexketoprofen administration

			TNF-α	IL-1	IL-6
NRS after administration	Dexketoprofen	R	-0,266	0,221	- 0,019
		P	0,219	0,311	0,932
		N	23	23	23

Discussion

At baseline, the mean of the NRS score was 4.86 ± 1.82 and became 1.96 ± 1.40 after Dexketoprofen administration. There was a significant decrement of the NRS score with $p = 0.001$. This fact suggests that Dexketoprofen is effective to lower the pain intensity in CTTH patients. Dexketoprofen is an (S)-enantiomer of ketoprofen. Ketoprofen racemic is an effective analgetic and anti-inflammatory agent and consider as a potent inhibitor of prostaglandin synthesis in vitro [7]. Dexketoprofen is a nonsteroidal anti-inflammatory drug which inhibits the cyclo-oxygenase one dan two enzymes (COX-1 dan COX-2) centrally and peripherally [8]. The facts that Dexketoprofen significantly decreased the pain intensity, but has no effect on the serum levels of TNF-α, IL-1 and IL-6 proved that these cytokines play non-significant roles in the pathophysiology of pain in CTTH patients. This study also found inconsistent correlations between NRS and TNF-α, IL-1 and IL-6 serum levels, furthermore, support the possibility of other mechanisms that may be responsible for pain generating process in CTTH patients.

Before Dexketoprofen administration, the mean of TNF-α serum level was 1.48 ± 0.65 pg/dl and became 1.48 ± 0.63 pg/dl after administration. There was a non-significant change of the mean of TNF-α serum level (p = 0.963). This data suggest that TNF-α serum level had no correlation with decreased pain intensity after Dexketoprofen administration in CTTH patients, differs from the previous study. A study by Bo *et.al* in 2008, showed significant differences between the CSF level of IL-1ra, TGF-β1 and MCP-1 in TTH and migraine patients when compared to the control group [3]. The non-significant result of TNF-α in this study is by several previous studies. Tanure *et.al.* found no significant difference in the level of TNF-α, sTNFR1 and sTNFR2 during a migraine attack and headache-free period [9]. In headache patients, the cytokines were only increased slightly if compared to other severe neurological diseases. This increment was considered as a slight response of cytokine toward a headache [10]. A study by Rozen et al. found an increment of TNF-α in CSF of New Daily Persistent Headache (NDPH) and migraine patients. But the increment was not found in serum [11]. TNF-α is the primary pro-inflammatory cytokine for brain infection diseases. In normal condition, this cytokine is produced in a very small quantity. In the state of infection, where there is a strong stimulation by microorganisms, the production will greatly increase so that it can be detected in blood with a quite significant level [12]. The non-significant finding in this study maybe due to the measurement of TNF-α was performed in the serum where more confounding variables found compare to CSF. The very low serum level of TNF-α found in this study was probably indicated that in CTTH patients, the only very small amount of TNF-α produced, in contrast with during brain infection.

There was a contradictory of significance in the result between NRS score and TNF-α serum level, before and after Dexketoprofen administration. With p = 0.001, Dexketoprofen effectively reduced pain intensity. On the other side, p = 0.963 after Dexketoprofen administration, suggest that TNF-α level was not significantly decreased as a result of Dexketoprofen administration. This fact suggests that pain intensity decrement due to Dexketoprofen administration was not through TNF-α decrement mechanism. Regarding pain, there were still many biological mechanisms of Dexketoprofen, which were still not fully understood [13]. Many in vitro studies regarding the effect of TNF-α on CNS has been performed, with still ambiguous conclusions [14]. Before Dexketoprofen administration, the mean level of IL-1 was 0.16 ± 0.80 and it became 0.26 ± 0.31 after administration (p = 0.168). This fact showed that IL-1 serum level did not significantly decrease pain intensity as a result of Dexketoprofen administration in chronic TTH patients. Together, IL-1 and IL-6 causes trigeminal nociceptor sensitization and play an important role in migraine pathogenesis by reducing sensitivity threshold toward other inflammatory stimulus [15]. As strong mediators for fever, pain, and inflammation, IL-1 and TNF-α function via hypothalamic induction [12, 16]. Research by Bo et al found an increment of cytokine IL-1, TGF-β1 and MCP-1 level in ETTH and migraine patients' CSF [3]. The non-significant result on the IL-1 level in this research was by previous studies. In normal condition, the IL-1 production is very small. In infection condition, where there is a strong stimulation by micro organisms, the production will greatly elevate so that it can be detected in blood with a quite significant level [12]. The small quantity of IL-1 in this study was caused by an inflammatory process such as in TTH and not an infectious process of the brain.

There was contradictory of significance in the result between NRS score and IL-1 serum level, before and after Dexketoprofen administration. With p = 0.001, it means that Dexketoprofen effectively reduced pain intensity. On the other side, p = 0.168 after Dexketoprofen administration, suggests that IL-1 level was not significantly different as a result of Dexketoprofen administration. This fact suggests that pain intensity decrement due to Dexketoprofen administration was not through IL-1 decrement mechanism. Regarding pain, there were still many biological mechanisms of Dexketoprofen, which were still not fully understood [13]. The correlation between IL-1 and Dexketoprofen in reducing pain intensity is still unclear.

Before drug administration, the level of IL-6 = 1.06 ± 0.83, and after administration, it became 1.04 ± 0.81 with no significant difference between them (p = 0.915). This fact showed that IL-1 serum level did not significantly decrease pain intensity as a result of Dexketoprofen administration in chronic TTH. Interleukin-6 function as a pro and anti-inflammation, secreted by T-cell and acts as an initial response toward infection and trauma. This substance can penetrate the blood-brain barrier and initiates PGE_2in hypothalamus, thus elevating body temperature. Whenever infection occurs, production of IL-6 will increase [17]. Systemic effect of IL-1 will cause induction of fever, acute phase protein plasma synthesis by the liver, and directly stimulate the production of IL-6, and production of neutrophil and platelet in bone marrow [15]. In migraineurs, it has been suggested that IL-6 level increase during the headache phase. A study by Yan et al. showed that IL-6 strengthen excitability of dura mater afferent fibre so that sensitization which contributed toward a pathophysiology migraine headache occurred [18].

From statistical analysis, there was a non-significant difference of IL-6 level, with p = 0.915, after Dexketoprofen administration. The non-significant result of IL-6 in this study was supported by previous study results. The same as TNF-α and IL-1, IL-6 is very responsive toward infection [17]. Regarding pain in an animal experiment, IL-6 can stimulate trigeminal

ganglion cell to synthesise COX-2 and PGE2, which will release CGRP that causes pain [19]. Bo et al. did not reveal any significant difference in CSF level of several pro-inflammatory cytokines in TTH, migraine, and carcinogenic headache [3]. But, IL-6 pain-related detection in those studies was obtained through LCS, not serum.

There was contradictory of the result between NRS score and IL-6 serum level, before and after Dexketoprofen administration. With p = 0.001, it means that Dexketoprofen effectively reduced pain intensity. On the other side, p = 0.915 after Dexketoprofen administration, suggest that IL-6 level was not significantly different as a result of Dexketoprofen administration. Regarding pain, there were still many biological mechanisms of Dexketoprofen, which were still not fully understood [13]. This fact suggests that pain intensity decrement due to Dexketoprofen administration was not through IL-6 decrement mechanism.

In these subjects, there was statistically significant decrement of pain intensity based on the mean of NRS score (p = 0.001), from 4.86 ± 1.82 (before) to 1.96 ± 1.40 (after). There was a non significant (p = 0.963) change of the mean of TNF-α serum level, from 1.48 ± 0.65 pg/ml (before administration) to 1.48 ± 0.63 pg/ml (after administration). As for IL-1 and IL-6 serum level, there was also non-significant difference between before and after administration (p = 0.168 and p = 0.915 respectively). After Dexketoprofen administration, TNF-α serum level had a weak negative correlation (R = -0.266) and non-significant (p = 0.219) with pain intensity. There was a weak, non-significant positive correlation (R = 0.221; p = 0.311) between pain intensity and IL-1 serum level and a very weak, non-significant correlation (R = -0.019; p = 0.932) between pain intensity and IL-6 serum level.

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Clinical Science

Gluten Sensitivity among Egyptian Infants with Congenital Heart Disease

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Abstract

BACKGROUND: Gastrointestinal symptoms are a common feature in infants with congenital heart disease.

AIM: This study was designed to evaluate age-dependent serum levels of antigliadin antibodies among malnourished Egyptian infants with congenital heart disease (CHD) and gastrointestinal symptoms.

SUBJECTS AND METHODS: This case-control study conducted on 60 infants with established congenital heart disease. They were subdivided into cyanotic and acyanotic groups, and each group includes 30 patients compared with thirty apparently healthy infants of matched age, sex, and social class. Serum antigliadin antibodies levels were measured using ELISA.

RESULTS: The mean age of introduction of cereals in the diet and appearance of gastrointestinal symptoms were six months. On comparison with controls, patients showed highly significant higher serum levels of antigliadin antibodies ($P < 0.000$). On analysing risk factors using odds ratio, the age at onset of GIT symptoms, diarrhoea, abdominal pain, and distension had been found to be significantly associated with high serum antigliadin antibodies among malnourished CHD infants with a prediction of 95%.

CONCLUSION: Serum IgA, IgM, and IgG class antibodies to gliadin play a significant role in the pathogenesis of malnutrition in infants with CHD. Gluten containing foods should never be introduced before the end of the six months.

Introduction

Congenital heart diseases (CHD) are documented in 0.8 % of all live birth infants. They are characterised by gross structural abnormalities of the heart or the great vessels that interfere with normal cardiac function [1]. Malnourished infants with CHD showed growth retardation, frequent hospitalisation, poor surgical outcomes and higher mortality rate [2]. They also showed poor food intake, malabsorption, increased requirements, and higher metabolic rate in the first year of life [3]. Retarded growth was accompanied by frequent diarrhoea attacks and infectious diseases [4].

Gliadin is part of the gluten protein found in the grains wheat, barley, rye, and oats. It is a unique protein based on its structure that lends a doughy, elastic consistency to flours derived from these grains. Some children have gluten protein intolerance, which may be attributed to enhanced T-cell-mediated immune reaction in the proximal small bowel that damages the villi of the small intestine and leads to nutrients malabsorption [5]. The inflammatory response continues as long as patients continue to ingest protein [6]. The Gluten sensitivity usually manifests in childhood, and symptoms include failure to thrive, diarrhoea, and abdominal pain. Subclinical cases may have no overt gastrointestinal symptoms but suffer osteopenia, anaemia, and irritability [7, 8].

Studies to date regarding the immune response to gluten in infants with CHD and its association with gluten sensitivity have been

inconsistent. Therefore, this study was planned to evaluate age-dependent serum levels of IgA, IgG, and IgM antigliadin antibodies among malnourished Egyptian infants with CHD and gastrointestinal symptoms and to investigate if these antibodies have any relation to growth, nutritional status, and gastrointestinal symptoms.

Subjects and Methods

Design and Setting of the study

This case-control study was conducted on 60 infants with congenital heart disease (CHD) and recurrent gastrointestinal symptoms (40 % girls and 60% boys) who were attending the Nutrition Clinic of the Center of Excellence, National Research Center (NRC) for nutritional management of malnourished patients with CHD over a period of one year according to inclusion criteria. They were referred from the outpatient Pediatric Cardiology Clinics of the National Cardiac Institute, Egypt, during their regular follow up. The sample size was calculated to detect the mean differences in the scores of the factors probably affecting growth, nutritional status of infants with congenital heart disease (CHD).

Subjects

Congenital cardiac defects were diagnosed by two-dimensional echocardiography. They were classified into two subgroups according to the presence or absence of the cyanosis into two subgroups; thirty cyanotic patients in subgroup I, and thirty acyanotic patients in subgroup II compared with thirty apparently healthy infants of matched age, sex, and social class. The inclusion criteria for selection included malnourished infants with uncorrected symptomatic congenital cardiac defects and history of gastrointestinal symptoms. The exclusion criteria included infants with palliated or corrected CHD, confirmed or suspected genetic syndromes, hospitalised, and infants with asymptomatic CHD. Written informed consent was obtained from the parents of the participating infants.

Methods

Information on age, parental consanguinity of CHD, duration of illness and treatment modalities were collected via a questionnaire from parents. All the studied patients were subjected to through history taking, including onset of the cyanosis, hypercyanotic spells, tachypnea, feeding difficulty, poor weight gain, repeated chest infections, gastroenteritis, and congestive heart failure. Patients and controls were subjected to a complete physical examination, nutritional assessment, anthropometric measures, and laboratory investigations that were done at the National Research Center.

The anthropometric measures included measurement of body weight, recumbent length or height, body mass index (BMI), occipitofrontal, mid-arm, and mid chest circumferences. The body weight was determined to the nearest 0.1 kg on a sea scale balance with the subject dressed minimum clothes and no shoes. Heights or recumbent length (for infants <2 years of age) were measured using Seca mechanical infantometer. The mid-upper arms, mid-chest and occipitofrontal circumferences were measured with a measuring tape using standard procedures. Each measurement was taken as the mean of three consecutive readings as recommended by the International Biological program [9].

The anthropometric analysis for all infants was accomplished through the calculation of Z-scores, based on the WHO growth standards [10], and Anthro 2007© software [11]. Z-scores were calculated for the following rates: weight/age, weight/length, length /age. The following were adopted as cut-off points for the z-values: normal values between two units of a standard deviation below and above the average value. In all cases, a Z-score of less than -2 was considered as the cut-off point for malnutrition. Values between ± 1 and ± 2 SD units of standard deviation constituted the zone of risk.

Biochemical measurements

From all cases, and controls five cc venous blood samples were obtained for laboratory assays, which were performed in the National Research Center. Serum antigliadin IgA, IgG, and IgM antibodies levels were measured by enzyme-linked immunosorbent assay (ELISA) commercial kit according to the method of Trocone and Ferguson [12]. The cutoff value was calculated from healthy control samples.

Serum calcium concentration was assayed by a colorimetric method according to the method described by Endres and Rude [13]. Samples for assaying serum alkaline phosphatase activity (ALP) were kept at room temperature and assayed according to the manufacturer's guidelines [14]. Haemoglobin level was measured using Hemoglobin Photometer [15]. Serum iron and total iron binding capacity were measured according to the method described by Perrotta and Kaplan [16].

Statistical analysis

Statistical analysis was performed using the SPSS statistical package software for Windows version 21 (SSPS Inc, Chicago, USA) and the results were presented as tables and figures. Quantitative

variables are expressed as the mean ± SD.

Categorical data were expressed as frequencies and percentages and were analysed with the two-tailed chi-square test. Correlations between continuous variables were done using Pearson correlation. The comparison between groups was performed with one-way analysis of variance (ANOVA). Univariate analysis of each covariate (item by item) was performed to identify significant of high serum levels of antigliadin antibodies in malnourished patients with CHD and gastrointestinal symptoms. A P value < 0.05 was considered significant and p < 0.005 was considered highly significant.

Results

This study comprised 60 patients with established CHD. Their ages ranged from 4-12 months (mean 8.72 ± 6.68 months) were enrolled in the present study. They were 36 boys (60 %) and 24 girls (40%) with a male to female ratio 1.5:1. Cyanosis was detected in 30 patients (50%). About 60% of the studied patients were on bottle feeding, and 40% patients were breastfed.

Cereals were introduced at a mean age of 6 months (ranging from 4 to 8 months), and the mean age of onset of gastrointestinal symptoms was six months. Such symptoms entailed chronic diarrhoea in 58 (96.7%), vomiting in 26 (43.3%), abdominal pain in 38 (63.3%), and abdominal distension in 14 (23.3%). Growth failure was seen in 48 patients (80%), pallor in 44 patients (73.3%), and rickets in 34 patients (56.7%). Thirty patients (50%) received anti-failure medications. All these clinical findings concerning the patient's group are shown in Table 1.

Table 1: Clinical findings of the studied patients

Variables	No (%)	Variables	No (%)
Male	26 (43.3%)	Pallor	44 (73.3%)
Female	34 (56.7%)		
Positive consanguinity	24 (40 %)	Rickets	34 (56.7%)
Diarrhea	58 (96.7%)	Repeated chest infections	12 (20%)
Vomiting	26 (43.3%)	Anti-heart failure medications	30 (50%)
Abdominal pain	38 (63.3%)	Abdominal distension	14 (23.3%)

The mean measurements of z scores of weight for age, weight for height, height for age, and the circumferences of occipitofrontal, mid arm, and mid chest of the studied patients were statistically highly significant lower compared to controls (P < 0.001). The mean weight for age, weight for height Z-scores, circumferences of occipitofrontal, mid arm of the cyanotic group were statistically significant lower about the acyanotic group (P < 0.05). Table 2 demonstrates the anthropometric measures of patients versus control.

Table 2: Comparison of anthropometric measures of the studied patients, and control groups

Variables	Total Patients N=60	Cyanotic subgpI n=30	Acyanotic subgpII n=30	Control Group N=30	subgpI versus subgpII	Total patients versus controls
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	P value	P value
Occipitofrontal circumference(cm)	42.93±3.59	41.53±3.86	44.33±2.76	46.4±3.55	0.03*	0.002**
Mid-arm circumference(cm)	12.2±1.66	11.43±1.69	12.97±1.27	13.49±0.9	0.002**	0.003**
Mid-chest circumference(cm)	44.0±4.38	43.27±5.2	44.73±3.42	49.85±3.31	0.32	0.000**
Weight for age z-score	-2.55±1.27	-3.18±0.9	-2.02±1.29	-0.25±0.42	0.003**	0.000**
Height for age z-score	-2.62±1.4	-3.07±1.28	-2.38±1.35	0.25±0.55	0.107	0.000**
Wt for Ht z score	-0.75±1.0	-1.34±0.88	-0.28±1.07	-0.24±0.65	0.001**	0.03*

*Significant difference at p<0.05, **highly significant difference at p<0.005.

The patients' group demonstrated a statistically highly significant increase in serum levels of IgA, IgM, and IgG class antibodies to gliadin on healthy controls (P < 0.000). ANOVA test revealed statistically highly significant rise in the serum levels of IgA, IgM, and IgG class antibodies to gliadin, alkaline phosphatase activity, total iron binding capacity, and statistically highly significant reduction in blood hemoglobin, serum calcium and iron levels between the patients' subgroups and controls with the lowest value in the cyanotic group (P < 0.001) as shown in Table 3.

Table 3: Comparison of laboratory findings of the studied patients, and control groups

Variables	Cyanotic subgroup I n=30	Acyanotic subgroup II n=30	Control Group N=30	ANOVA	
	Mean ±SD	Mean ±SD	Mean ±SD	F	P
Serum antigliadin IgA (IU/ml)	151.95±59.4	150.81±27.84	92.07±2.67	104.17	0.000**
Serum antigliadin IgG (IU/ml)	111.95±109.83	142.16±138.57	70.77±17.51	1.4	0.251
Serum antigliadin IgM (IU/ml)	3.9±2.63	2.8±1.52	1.1± 0.33	431.96	0.00**
Serum calcium (mg/dl)	8.35±0.23	8.46± 0.52	9.38±0.29	31.35	0.00**
Serum alkaline phosphatase (IU/l)	336.53±84.1	380.71±110.56	106.4±14.38	66.702	0.00**
HB (gm/dl)	13.78 ± 1.8	11.54 ± 1.7	13.05 ± 0.77	5.495	0.007**
Serum iron (mcg/dl)	40.56±8.03	33.40±6.10	73.5±8.75	138.22	0.00**
Serum TIBC (mcg/dl)	432.0±14.52	388.53±37.44	285.4±27.4	109.28	0.00**

*Significant difference at p<0.05, **highly significant difference at p<0.005.

In the patient's group, serum IgM levels showed significantly negative correlation with serum calcium levels, and height for age z- score (P < 0.05). Serum antigliadin IgG levels were significantly positively correlated with serum alkaline phosphatase activity, and negatively correlated with z- score of weight for age. Correlations between anthropometric measures and serum antigliadin antibodies of the studied patients are shown in Table 4.

Table 4: Correlations between weight and height for age z-score, some laboratory measures and serum antigliadin antibodies of the studied patients

Variables	Weight/age z-score	Height / age z-score	Serum calcium	Serum alkaline phosphatase
Serum antigliadin IgM (IU/ml)	-0.107	-0.265*	-0.331*	0.117
Serum antigliadin IgG (IU/ml)	-0.261*	0.111	0.189	0.292*
Serum antigliadin IgA (IU/ml)	0.105	0.162	0.031	0.036

*Significant difference at p<0.05, **highly significant difference at p<0.005.

Table 5: Univariate analysis between GIT symptoms and serum antigliadin IgA antibodies levels in the studied patients

Covariates		Serum antigliadin antibodies (IgA) High 26 (60%) No %	Normal 34 (40%) No %	P value	Odd ratio (95% CI)
Age at onset of symptoms	Before 6 month	8 (30.8%)	22 (64.7%)	0.04*	4.13 (0.88,19.27)
Diarrhea	Negative	4 (15.4%)	26 (76.5%)	0.02*	0.06 (0.01, 0.37)
Abdominal pain	Positive	20 (76.9%)	22 (64.7%)	0.01*	0.55 (0.11, 2.80)
Abdominal distension	Positive	20 (76.9%)	10 (29.4%)	0.01*	0.13 (0.02, 0.66)

*Significant difference at $p < 0.05$, **highly significant difference at $p < 0.005$. Gastrointestinal symptoms (GIT).

On analysing risk factors using odds ratio, the age at onset of gastrointestinal symptoms in the form of diarrhoea, abdominal pain and distension were documented as a significant association of raised serum levels of antigliadin antibodies in the patients with a prediction of 95% as shown in Tables 5, 6, 7.

Table 6: Univariate analysis between GIT symptoms and serum antigliadin IgG antibodies levels in the studied patients

Covariates		Serum antigliadin antibodies (IgG) High 12 (20%) No %	Normal 48 (80%) No %	P value	Odd ratio (95% CI)
Age at onset of symptoms	Before 6 month	16 (38.1%)	14 (77.8%)	0.04*	5.69 (0.94, 34.46)
Diarrhea	Negative	0 (0%)	30 (62.5%)	0.02*	0.06 (0.01, 0.37)
Abdominal pain	Positive	10 (83.3%)	32 (66.7%)	0.01*	0.55 (0.11, 2.80)
Abdominal distension	Positive	12 (100%)	18 (37.5%)	0.01*	0.13 (0.02, 0.66)

*Significant difference at $p < 0.05$, **highly significant difference at $p < 0.005$. Gastrointestinal symptoms (GIT).

Discussion

The poor growth seen in infants born with complex heart defects may result from factors beyond deficient nutrition [17]. The cause is not yet identified. However, it may be a consequence of a disordered immune response to gliadin proteins in genetically predisposed infants or may be attributed to the early introduction of cereals in the infant's diet before the age of 6 months, yielding higher levels of antibodies against such proteins [6]. There are three types of antigliadin antibodies, IgA, IgM, and IgG. IgA antibody is specific, and the IgG antibody is a sensitive marker of gluten sensitivity.

Table 7: Univariate analysis between GIT symptoms and serum antigliadin IgM antibodies levels in the studied patients

Covariates		Serum antigliadin antibodies (IgM) High 42 (70%) No %	Normal 18 (30%) No %	P value	Odd ratio (95% CI)
Age at onset of symptoms	Before 6 month	20 (38.1%)	14 (77.8%)	0.04*	5.69 (0.49, 4.46)
Diarrhea	Negative	20 (47.6%)	10 (55.6%)	0.60	0.73 (0.15, 3.49)
Abdominal pain	Positive	10 (83.3%)	2 (11.1%)	0.00**	0.01 (0.00, 0.11)
Abdominal distension	Positive	26 (61.9%)	4 (22.2%)	0.04*	0.18 (0.03, 1.07)

Measurement of the combined antibodies provides a specificity of 84% and a sensitivity of 94% for the diagnosis of gluten sensitivity disease [18].

Up till now, there is no available information in the literature regarding the presence of serum antigliadin antibodies among malnourished infants with congenital heart diseases.

Our study comprised sixty patients suffering from CHD. They were diagnosed by clinical examination, echocardiography, and other routine tests. Such patients were further subdivided into acyanotic and cyanotic subgroups. The commonest cyanotic lesions were tetralogy of Fallot (TOF) and transposition of the great arteries (20% in each). Almost 5 % of our patients suffered from pulmonary atresia with ventricular septal defect (VSD), and 5 % presented with double outlet right ventricle (DORV) with malposed great vessels.

Ventricular septal defect (VSD) was the most frequent acyanotic lesions (20%), 15% of our patients were diagnosed as patent ductus arteriosus (PDA), 10% as atrial septal defect (ASD), and 5% as an atrioventricular canal (A-V canal).

About 60% of our patients were on mixed feeding, and 40% patients were breastfed. Cereals were introduced at a mean age of 6 months (ranging from 4 to 8 months) and mean age of onset of gastrointestinal symptoms was six months. Such symptoms included chronic diarrhoea in (96.7%), vomiting in (43.3%), abdominal pain in (63.3%), and abdominal distension in (23.3%). Growth failure was seen in (70%), pallor in (73.3%), and rickets in (56.7%) of patients. The earlier onset of gastrointestinal symptoms in our studied patients was not in agreement with Assiri et al., [19] who found that, gastrointestinal symptoms started at a mean age of 57.2 months (ranging from 4 to 156 months) and manifested in 54% as chronic diarrhea, in 22.2% as vomiting, in 17.5% as abdominal pain, and in 3.2% patients as abdominal distension. Growth failure was detected in 74.6% patients. The early introduction of cereals in our patients may be responsible for the early appearance of gastrointestinal symptoms.

In view of our data, the mean measurements of z-scores of weight for age and height for age, weight for height, as well as the circumferences of occipitofrontal, mid arm, and mid chest of the patients group showed statistically highly significantly decrease when compared to controls ($P < 0.001$), and statistically significantly lower in cyanotic group than acyanotic group ($P < 0.05$). Severe malnutrition was found in thirty-three (55%) of the studied patients, while moderate malnutrition was shown in twenty-seven (45%). Thirty-six (60%) of our patients manifested a decreased WHZ (wasting), which was proportionately more documented in the cyanotic group ($P < 0.001$). Our results are in agreement with WHO reports, which demonstrated that malnutrition manifests mainly as wasting rather than underweight and stunting [20].

Studies concerning malnutrition patterns amongst patients with CHD yielded incontinent results

(21-23). In South India, Vaidyanathan et al., [21] recorded underweight in (59.0%) with wasting being more evident than stunting in infants suffering from CHD. These results came from our data. El-Alameey et al., [22], and Varen et al., [23], stated that wasting was more common in cyanotic CHD than in acyanotic CHD.

Anaemia is an important risk factor for morbidity and mortality among infants suffering from CHD (cyanotic and acyanotic) in the absence of vitamin or mineral deficiency, or hemolytic causes [24]. More than 30% of the patients with CHD had iron deficiency anaemia [25]. It may co-exist and worsen acyanotic CHD heart failure [26].

Iron deficiency anaemia was evidenced in 73.3 % of our patients with a statistically highly significant increase in serum levels of total iron binding capacity compared to control group ($P < 0.000$).

By our study, Assiri et al. [19] found. Also, rickets was present in 6 patients (10%), it may be secondary to calcium deficiency, or intestinal malabsorption.

Our patients demonstrated statistically highly significant increased serum alkaline phosphatase activity and decreased serum levels of calcium than the control group ($P < 0.000$).

Gluten sensitivity leads to raised serum level of anti-gliadin IgA and IgG antibodies. Antigliadin IgA antibodies are more specific markers for disease than antigliadin IgG antibodies serving for initial screening, assessing diseases activity, and judging management with a gluten-free diet [6].

To our knowledge, the present study is the first to document raised serum levels of antigliadin antibodies in malnourished infants with CHD and gastrointestinal symptoms. Forty-two patients with CHD had statistically significant higher levels of IgM antibody to gliadin, twenty-six patients exhibited a significant elevation of the serum levels of IgA anti-gliadin antibodies and twelve patients demonstrated significantly increased serum levels of IgG antigliadin antibodies compared to control group ($P < 0.000$). A statistically highly significant elevation of the serum levels of IgA, IgM, and IgG antigliadin antibodies was evidenced in our studied patients compared to control group ($P < 0.000$). On analysing risk factors using odds ratio, the age at onset of gastrointestinal symptoms in the form of diarrhoea, abdominal pain and distension were documented as a significant strong association of raised serum levels of antigliadin antibodies in the infants with CHD with a prediction of 95%.

In our patients, serum antigliadin IgM levels were significantly negatively correlated with serum calcium levels and height for age z- score ($P < 0.05$). Serum antigliadin IgG levels were significantly positively correlated with serum alkaline phosphatase activity, and negatively correlated with z- score of weight for age. These data indicated that when serum levels of antigliadin IgM, and IgG increased, more stunting and underweight was found.

Interestingly, our study showed clinical improvement of some patients on the exclusion of gluten from the diet and continuing of breastfeeding. Rapid recovery was reported concerning weight gain. Breastfeeding protects against repeated episodes of acute gastroenteritis which have been linked to increased risk of gluten sensitivity. This reduction could be mediated via immunoglobulins present in human milk [27, 28].

From the current findings, it could be concluded that serum IgA, IgM, and IgG class antibodies to gliadin play a significant role in the pathogenesis of malnutrition.

Breastfeeding is protective, may be beneficial in delaying or preventing gluten sensitivity. Babies born with CHD must be breastfed for at least one ear. Gluten containing foods should be avoided for the first 8th months of life.

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Clinical Science

Character and Temperament Dimensions in Subjects with Depressive Disorder: Impact of the Affective State on Their Expression

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Abstract

BACKGROUND: The depression is a cross-cultural condition that occurs in all cultures and within all nations with certain specificities, even though there are some differences in its manifestation. The hereditary load is of major importance, but also the individual personality factors, in the form of risk factors, are associated with the occurrence of depression. Personality characteristics have a significant impact on the occurrence of the recurrent depressive disorder and the outcome of the treatment as well.

AIM: To identify the specific personality traits in people with the recurrent depressive disorder and the impact of the affective state on them.

METHODS: Three questionnaires were used: a general questionnaire, Beck's scale of depressive symptoms, and TCI-R (inventory for temperament and character).

RESULTS: The most indicative differences in the dimensions are found in the Harm avoidance and the Self-direction dimensions, and most variable dimensions dependent on effective state are Novelty seeking and Reward dependence.

CONCLUSION: The people with the recurrent depressive disorder have a different profile of personality traits (temperament and character) compared with the control group, and their characteristics depend on their current affective state.

Introduction

Cloninger has created a theory of personality as a biopsychosocial model of temperament and character, which is derived out of biological, neurophysiologic, genetic and psychological studies [1, 2]. It describes the relationship between the biogenetic structure of personality and the mental disorders. Cloninger showed that the phenotypic personality structure might differ from the biogenetic structure, i.e. the impact of the behaviour as a result of the genotypic and environmental impacts. The main features of personality are temperament and characters dimensions.

While the temperament is largely genetically determined and configures automatic behavioural responses, the character develops during the ontogenetic with a major affection of the social factors and it delineates the cognitive processes of sensory perception and emotions that are oriented by temperament.

The temperament reflects the biological and the inherited features, and the character reflects the social and cultural contribution of the person. The role of the main functions of the person is to integrate the cognitive and the emotional features regarding adequate social functioning [3]. It is accepted that a personality plays an important role not only in the maintaining of well-being but also in the development of psychopathological conditions [4, 5].

The temperament is largely genetically determined and configures automatic behavioural responses. It consists of four hereditary dimensions that are visible from the early childhood and includes procedural and unconscious learning. They are identified as Novelty seeking (NS); Harm avoidance (HA); Reward dependence (RD); and Persistence (P).

The NS is a system of behaviour associated with activation by dopamine as their neurotransmitter. NS is expressed as a tendency toward excitement, curiosity, enthusiasm and impulsiveness. HA is a system of behaviour associated with inhibition with GABA and serotonin neurotransmitters. HA is a tendency associated with cautiousness, tension, irritability and pessimism. RD system is a system associated with serotonin and norepinephrine as its neurotransmitters. RD is a tendency to a sensitivity of warmth, sensibility, dependence and conviviality. P is a system of active behaviour in spite of the fatigue and the frustration, with glutamate and serotonin as its neurotransmitter [2].

The Character develops during ontogenesis with a great influence from the social factors. The character regulates the cognitive processes of the sensory perception and emotions that are targeted by the temperament. It consists of the following dimensions: Self-directedness (SD); Cooperativeness (CO); and Self-transcendence (ST).

These dimensions are determined more by the environment than they are inherited. The SD refers to identification with the autonomous self and ability for the solution of situations by the individual goals and values. The CO indicates the extent to which the individuals perceive other people as part of the self. The ST corresponds to the identification with a unity of all things in the world [2]. Each of these dimensions consists of dimensions of a lower order, i.e. sub-dimensions.

Relation of the temperament dimensions and the character with the depressive disorder

The personality model according to the Cloninger is quite adequate for clinical use, as in the assessing the risk processes of incidence of a depressive disorder and also in the process of planning an appropriate anti - depression treatment [6]. Several studies demonstrate that a high HA is associated with an onset of a depressive disorder, and the inherited vulnerability to depression is associated with a high HA and a low SD [7-9].

There is evidence that in the depression patients with an HA dimension, it remains elevated when compared to healthy controls during a remission [10, 11]. Farmer identifies RD together with the HS as factors that reduce the risk of major depression [12].

The main goal of this work is to determine the personality traits in people with the recurrent depressive disorder, as well as the impact of the affective state on these same features.

Methods

Research Instruments

Three questionnaires were used in this research: (1) A general questionnaire; (2) Beck's depressive symptoms questionnaire - second edition (BDI-II; Beck et al., 1996) [13, 14]; and (3) TCI - Inventory for temperament and character [15].

Time frame and research location

This research was conducted at the University Psychiatric Clinic - Skopje within a period of six months as a "case-control" study.

Experimental group (EG)

Twenty people diagnosed with the recurrent depressive disorder, with a score over 19.

Control group (CG)

Twenty psychologically healthy individuals were included as control group.

Results

Regarding the general questionnaire, the results for similar demographic determinants are obtained in both groups.

The results of the logistic regression show that the gender of the screened population is a significant predictor for the occurrence of the recurrent depressive disorder, with an incidence of more than 1.9 times in women than in men (OR = 0.902, p = 0.045) (Table 1).

The marital status is associated with the appearance of recurrent depressive disorder, by 1.5 times more likelihood among divorced respondents (OR = 1.563, p = 0.035). The likelihood of recurrent depressive disorder is 4.23 times higher among respondents who live alone (OR = 4.230, p = 0.042) and 5.2 times higher among respondents who have marked the marital status as "other" (OR = 5.221, p = 0.032) (Table 1).

Table 1: Results of logistic regression of demographic data as predictors for the occurrence of depressive disorder

	S.E.	Wald	p	OR	95% C.I. Lower	Upper
Gender						
Male				1		
Female	0.361	0.115	0.047*	0.884	0.0436	0.896
Education						
University degree		2.616	0.455	1		
High school degree	0.392	2.420	0.120	1.840	0.854	3.966
Elementary school degree	0.523	0.859	0.354	1.624	0.582	4.530
Without education	2842.722	6.309	0.999	4.363	0.000	5.213
Marital status						
Married		4.894	0.298	1		
Divorced	0.482	0.858	0.035	1.563	0.608	4.017
Partner	0.574	1.816	0.178	2.168	0.703	6.685
Single	0.711	4.119	0.042	4.230	1.051	17.028
Other	1.602	1.065	0.032	5.221	0.226	120.535
Employment status						
Employed		12.810	0.330	1		
Unemployed	0.411	0.947	0.005	1.492	0.667	3.340
Retired	0.646	10.117	0.001	7.815	2.201	27.742
Social support	0.791	4.427	0.035	5.277	1.121	24.850
Habitat (Live with)						
Spouse		14.956	0.292	1		
Partner	0.525	10.870	0.001	0.177	0.063	0.495
Family	0.552	12.811	0.000	0.139	0.047	0.409
Friends	1761.405	0.000	0.999	2.063	0.000	-
Alone	1.319	1.108	0.005	2.249	0.019	3.308
Constant	0.354	0.203	0.653	1.173		

Regarding the personality features, the following results are confirmed (Table 2):

NS - is with a medium value of 93.40 ± 5.54 SD before treatment, 96.23 ± 6.02 SD after treatment, CG medium score is 104.70 ± 6.95 SD - a statistically significant difference.

HA - Highly statistically significant differences for HA with values before the treatment (113.39 ± 15.10 SD), after the treatment 106.30 ± 7.47 SD and CG (93.71 ± 9.01 SD).

Table 2: Personality characteristics

Characteristic	Group	Mean ± SD	p
Novelty Seeking (NS)	EG1*	93.40 ± 5.54 SD	0.004
	EG2	96.23 ± 6.02 SD	
	CG	104.70 ± 6.66 SD	
Harm Avoidance (HA)	EG1	113.39 ± 15.10 SD	0.001
	EG2	106.30 ± 7,47 SD	
	CG	93.71 ± 9.01 SD	
Reward Dependence (RD)	EG1	99.14 ± 6.10 SD	0.008
	EG2	101.97 ± SD 7:01	
	CG	105.97 ± 6.06 SD	
Persistence (P)	EG1	114.42 ± 9.49 SD	0.126
	EG2	116.83 ± 10.64 SD	
	CG	117.18 ± 10.77 SD	
Self – Directedness (SD)	EG1	122.45 ± 7.13 SD	0.001
	EG2	137.75 + 8:49 SD	
	CG	141.87 ± 8.62 SD	
Cooperativeness (CO)	EG1	124.50 ± 8.09 SD	0.095
	EG2	127.30 ± 7.55 SD	
	CG	128.38 ± 7.71 SD	
Self –Transcendence (ST)	EG1	73.84 ± 5.35 SD	0.223
	EG2	71.54 ± 6.56 SD	
	CG	71.32 ± 7.60 SD	

*, EG1 = Experimental Group (time 1); EG2 = Experimental Group (time 2); CG = Control Group. Time 1 – At the beginning of antidepressant treatment; Time 2 – After 3 month's antidepressant treatment.

RD - Statistically significant differences were found in RD, 99.14 ± 6.10 SD before treatment, 101.97 ± SD 6.52 after treatment and the highest average of 105.97 ± SD 6.06 respondents from CG.

P - Statistically significant difference between the groups has not been found for the values of P: before treatment (114.42 ± 10.46 SD) 116.83 ± 10.64 SD after treatment, at the respondents from the CG (117.18 ± 10.15 SD) and p = 0.126.

SD - Highly statistically significant SD of all five components: 122.45 ± 7.13 SD before treatment 137.75 ± 8.49 after treatment, and at the CG (141.87 ± 8.62 SD).

CO - The difference between the average values is not statistically significant for the feature C: 124.50 ± 8.09 SD before the treatment, 127.30 ± 7.55 SD after the treatment and 128.38 ± 7.71 SD in CG (p = 0.095).

ST - not determined statistically significant differences in the total number of CT: before treatment 73.84 ± 5.35 SD after treatment 71.54 ± 6.56 SD and at the CG (71.32 ± 7.60 SD) (p = 0.223).

Discussion

According to the obtained results, it is evident that most of the personality dimensions are variable during the antidepressant treatment, i.e. that the affective state has a strong influence on their expression. Behaviour that is marked by high scores of the dimension 'Harm avoidance' is typical for people who suffer from depression, with exceptionally high scores during the depressive episode but also during its remission. On another hand, lower scores on the 'Self-direction' dimension are also typical for people with depression, and although the scores after the depressive episode are rising, yet it remains with a significant difference compared to the CG.

Also, the scores of the other personality dimensions 'Novelty Seeking' and 'Reward Dependence' are with significant changes regarding the affective state of the respondents, i.e. during the depressive episode, as well as after it, with converging values to the ones of the CG [10, 17]. These results confirmed also throughout many other international types of research, put the high values of these features in a group of significant protective factors for the appearance of a depressive disorder [16]. In other words, the people with high levels of 'Novelty Seeking' and 'Reward Dependence', are with a lower risk of developing a depressive symptomatology [18].

According to Cloninger, as well as many other researchers, the changes to certain dimensions have specificity for the depressive disorder, i.e. the change trends are typical for the people who suffer from depression [6]. It primarily refers to the features of HA and of the SD. The features of the person may have common grounds with the depression features, i.e. they may be predisposing factors for them to have an impact on the recurrent episodes of the illness, as well as to the changes in the clinical picture of the disease

[19, 20]. These features should not be considered independently, but their interaction should always be acknowledged and their mutual influence with the other personality features. The characteristics of a person can be grounds for the emergence of depressive disorder, i.e. they may be predisposing factors for them to have an impact on the recurrent episodes of illness, as well as changes in the clinical picture of the disease. And our study confirms the findings of many scientific studies have found that personality characteristics influence the expressions of symptoms, and vice versa, they are dependent on the characteristics of episodes of depressive disorder [21, 22]. Regarding socio-economic aspects of respondents in experimental group before and after treatment as compared to the control group, the conclusion is that they have the great mutual influence to the emergence of depression and, conversely, the impact of the depressive disorder on socioeconomic parameters of respondents. Taking into consideration these outcomes, recommendations can be made for practical application of the received results regarding individualised therapy solutions, which would be with a higher expected success percentage.

In conclusion, people with depressive disorder have specific differences in personality dimensions; the specific personality dimensions of the temperament and the character are variables depending on the affective state of the individuals; the high levels of HA and the low of SD are the most specific characteristics for individuals with depressive disorder, which are moderately variable throughout the depressive episodes; RD and NS are dependent affective dimensions, with significant variability during the depressive episodes, i.e. with similar features like the ones of the control group after the treatment; P, CO and ST are the least variables dependent on the affective state during the depressive episodes; according to the established variability of the personality features in the people with a recurrent depressive disorder, the following researchers shall be focused on the practical application of these findings to improve the individualized therapeutic approach.

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Stomatology

sTNF-R Levels: Apical Periodontitis Linked to Coronary Heart Disease

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Abstract

BACKGROUND: Different studies have implicated the exposure to systemic conditions in the aetiology of cardiovascular diseases like chronic inflammation including chronic periodontitis.

AIM: The present study has been conducted to examine whether biomarker sTNF-R was elevated in apical periodontitis as sTNF-R is a systemic marker of inflammation and has been identified as risk factors for cardiovascular diseases.

MATERIAL AND METHODS: sTNF-R levels were measured in 52 patients with apical periodontitis (M:F::25:27), aged 20-45 years and in 20 control patients without periodontitis (M:F::10:10, aged 20-48 years). Measurement of sTNF-R1 and sTNF-R2 was carried out in duplicate with standardised, commercially available enzyme immunoassays (R&D Systems Europe, Abingdon, UK).

RESULTS: The mean sTNF-R1 and sTNF-R2 levels in periodontitis were 820 (240) pg/ml (413 – 1620 pg/ml) and 1309 (403) pg/ml (540 – 2430 pg/ml), while in normal sTNF-R1 and sTNF – R2 levels were 740 (340) pg/ml (407-1240 pg/ml) and 1283 (414) pg (480 – 2340 pg/ml) respectively. Results indicated a positive high relationship between cardiovascular markers such as sTNF-R1 and sTNF – R2 and apical periodontitis.

CONCLUSION: Elevated levels of sTNF-R1 and sTNF – R2 in apical periodontitis patients indicate an increased independent risk of coronary heart disease.

Introduction

Periodontal disease is a chronic infection of periodontal tissue characterised by the loss of attachment between tooth and bone, and by the bone loss. Epidemiological associations between periodontitis and cardiovascular disease have been reported [1, 2]. This association could be attributed to the direct action of periodontal pathogens or their products on endothelial cells through transient bacteremia or ultimately due to products of the inflammatory response [3-5]. Advanced stages of dental caries lead to apical periodontitis.

Periodontitis and atherosclerosis have complex etiologies, genetic and gender pre-dispositions and might share pathogenic mechanisms as well as general risk factors. Also, increased levels of chronic inflammatory marker CRP, serum LDL-C and t-PA (a parameter of endothelial function) have been related to increased cardiovascular risk [6-8].

Tumour necrosis factor (TNF-alpha) plays a key role in the initiation of the inflammatory response [9]. TNF-alpha has been linked with CVD risk factors, and with carotid intima – media thickness [10]. TNF receptors ($sTNFR_1$ and $sTNF\text{-}R_2$) are markers of TNF activity [11]. TNF has also been implicated in the pathogenesis of some cardiovascular diseases, including atherosclerosis, heart failure, myocardial infarction, myocarditis and cardiac allograft rejection, and vascular endothelial cell responses to TNF might underlie the vascular pathology in many of these conditions. This might be because TNFR1 and TNFR2 differentially regulate cardiac responses to TNF. In transgenic mice with TNF-induced cardiomyopathy, ablation of the TNFR2 gene aggravates heart failure and reduces survival, whereas ablation of TNFR1 blunts heart failure and improves survival [12, 13]. In

cardiac allografts either TNF receptor is capable of mediating a response that will culminate in graft arterial disease [14]. Patients with chronic inflammatory conditions such as rheumatoid arthritis have the higher incidence of cardiovascular disease. Inflammatory mediators, including TNF, have been concerned with higher cardiovascular risk, and there is some evidence that anti-TNF therapy ameliorates this risk in patients with rheumatoid arthritis [15-20].

A good correlation has been observed between saliva and serum concentrations of biomarkers [21]. Therefore sampling of saliva is advantageous since non-invasive, stress-free, easy and frequent collections are possible [21]. Hence, if periodontal disease is found to be associated with $sTNFR_1$ and $sTNF\text{-}R_2$, it might be a potential mediator for the association between apical periodontitis and CVD (Cardiovascular diseases).

Our study aimed to assess whether serum $sTNFR_1$ and $sTNF\text{-}R_2$ was elevated in apical periodontitis as sTNF-R is a systemic marker of inflammation and has been identified as risk factors for cardiovascular diseases.

Material and Methods

The total sample of 72 patients was quantified into two groups. Out of 72 patients, fifty-two patients were diagnosed with apical periodontitis (M: F::25:27, aged 20-45 years. Twenty (M: F::10:10, aged 20-48 years) subjects with in normal periodontal condition were selected for control. One or more apical lesions due to dental caries in teeth with non-vital pulp were taken as diagnostic criteria of apical periodontitis [16]. Periodontal parameters such probing depth and clinical loss attachment were measured by William probe. Subjects were excluded from the study if they were the chronic alcoholic or chronic smoker since they are known predisposing factors for periodontitis. None of the subjects selected had any history of a chronic inflammatory disease, diabetes, hypertension or use of steroids or drugs.

From all subjects, 10 ml EDTA blood was sampled at before treatment. After cooling centrifugation (10 min at 4°C and 3000 revs/min), the plasma was frozen at -80°C in 250 ml aliquots for up to 30 days. sTNF-R1 and sTNF-R2 were analysed by ELISA kit. Measurement of sTNF-R1 and sTNF-R2 was carried out in duplicate with standardised, commercially available enzyme immunoassays (R&D Systems Europe, Abingdon, UK). The data was statistically analysed using SPSS version 11.0, and Student t-test was applied.

Results

There was no significant difference in socio-demographic status between two groups (Table 1).

Table 1: Socio-demographic characteristics of periodontitis and normal healthy

Variables	Number in %		P value
	Periodontitis subjects	Normal (control) subjects	
Age in years			0.076
17-25	33	30.1	
26-32	29.1	28.9	
More than 32	37.9	41	
Mean (SD)	29.45 (6.34)	29.34 (5.62)	
Education Status			0.726
Less than high school	41.6	45.9	
High school	31	27.4	
More than high school	27.4	26.7	
Job status.			0.789
Not employed	90.2	89.2	
Employed	9.8	10.8	

sTNF-R1 and sTNF–R2 levels and clinical periodontal profile were significantly higher in apical periodontitis patients as compared to normal patients without periodontitis (Table 2). The mean intra-observer agreement was 96.4%, and the mean inter-observer agreement was 94.2%.

Table 2: Different clinical parameters of periodontal profile and sTNF-R1 and sTNF-R2 levels in periodontitis and normal healthy control

	Periodontitis	Normal	P value
Average number of periodontal involved site	9.2 ± 1.2	2.0 ± 1.8	0.001
Average probing pocket Depth (in mm) (William probe)	6.3 ± 1.2	1.3 ± 1.2	0.001
Average clinical loss of attachment (in mm)	5.2 ± 1.3	1.7 ± 1.5	0.001
$sTNF\text{-}R_1$ (pg/ml)	820 ± 240	740 ± 340	0.03
$sTNF\ R_2$ (pg/ml)	1309 ± 403	1283 ± 414	0.04

Data observed that a positive significant relationship between sTNF-R1 and sTNF – R2 cardiovascular disease markers and periodontal disease clinical parameters markers such as an average number of periodontally involved site, probing depth and clinical loss of attachment (Table 3).

Table 3: Bivariate correlations between cardiovascular markers and Markers of periodontal in periodontitis patients (after adjusting the age and gender)

Variables	$sTNF\text{-}R_1$	$sTNF\text{-}R_2$
Average number of periodontal involved site	0.49	0.42
Average probing pocket (Depth)	0.49	0.43
Average clinical loss of attachment (in mm)	0.69	0.66

Discussion

Our study showed the correlation between apical periodontitis and cardiovascular marker TNF receptors. The $sTNF\text{-}R_1$ and $sTNF\text{-}R_2$ levels were considerably higher in periodontitis patients as compared to normal patients without periodontitis. TNFα is one of the major pro-inflammatory cytokines [10-13]. It's role in the pathogenesis of chronic

inflammatory diseases has been long established, and serves as a source for the novel anti-cytokine therapies lately introduced [10]. An increased TNF secretion without corresponding higher levels in sTNFR shedding advocates a relative deficiency in sTNFR and an increase in the bioavailable TNF. This secretion disproportion between TNF and its soluble receptor had been detected in some chronic inflammatory disorders and had been implicated in their pathogenesis [10-11]. Previous studies reported that no associations between periodontal disease and TNF receptors [10]. This might be due to small sample size or less inflammation observed in the studies.

TNF-alpha has been associated with CVD risk factors, and with carotid intima-media thickness [11]. It has been observed that genetic variation at gene locus for TNF-alpha affect the risk of preterm birth independently and as interacting factors [12-15]. Many Studies found that levels of these biomarkers during acute infection revealed levels of sTNF-R ten-fold or greater than those reported in the present study. While differences were statistically significant [13-17], but the clinical significance of these differences was not observable. This could be attributed to the fact that periodontal infection was not so acute and severe as compared to the cardiovascular disease.

TNF-α is a potent inflammatory cytokine. The main source of TNF-α is activated mononuclear leukocytes, though it is concealed by a broad variety of other immune and nonimmune cell types, including fibroblasts, smooth muscle cells, astrocytes, and neurones [15]. TNF receptor 1 (also known as p55) and TNF receptor 2 (also known as p75) are both soluble receptors discard by different cell types on which they reside [15, 16, 18]. Elevation of TNF-α and TNF receptor levels occurs in a variety of infectious, autoimmune, inflammatory, and neoplastic diseases. Elevated levels of TNF receptor might be a reflection of the inflammatory mechanisms operative in the atherosclerotic plaque. Macrophages and T-lymphocytes are important in human atheromas, still at the earliest stages of the disease process [16, 17], suggesting that immune processes might play an early role in the development of the lesion in human beings. Our data provides evidence for at least a partial role for activated leukocytes in the chronic process of periodontitis. It has been demonstrated that patients with advanced CHF had increased concentrations of circulating TNF, especially those who were cachectic. Numerous studies have confirmed that CHF is a state of inflammatory cytokine activation [18]. It has been speculated that the association between elevated levels of inflammatory markers and periodontitis reflects chronic subclinical infection, although this hypothesis awaits confirmation. Several observational epidemiological studies [18-20], have suggested an association between chronic infections such as Chlamydia pneumonia and periodontitis and stroke risk or carotid atherosclerosis. Nonetheless, the elevations in TNF receptor levels seen here could also be related to the presence of other noninfectious stimulants of inflammation. Further prospective studies of the relationship between TNF receptors and other inflammatory and infectious markers are needed. While many investigators have examined the relationship between inflammation, infection, periodontitis and atherosclerotic heart disease, these may not reflect the relationship between these processes and stroke. Further study is required on a large scale while considering the risk factors and effect of apical periodontitis treatment on TNF receptor levels.

In conclusion, elevated levels of sTNF-R1 and sTNF–R2 in apical periodontitis patients indicate an increased independent risk of coronary heart disease.

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Stomatology

Bone Height Changes of the Mandibular Edentulous Ridge in Screw Retained Versus Telescopic Restorations for Completely Edentulous Patients

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Keywords: Dental implants; screw retained; telescopic overdenture; bone height; index area; mandible.

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Abstract

AIM: This study was established to evaluate the amount of bone height changes in the posterior mandibular area of edentulous patients receiving screw-retained prostheses versus removable telescopic implant overdentures.

MATERIAL AND METHODS: Every patient received four inter-foraminal implants regarding the mandibular arch and four anterior implants for the maxillary arch, computer guided surgical guides were planned for the insertion of the implants accurately with a flapless technique. Panoramic radiographs were made immediately, six months and twelve months after the prostheses` use proportional area and vertical measurements were applied to determine changes in the bone height of the posterior mandibular edentulous area.

RESULTS: After twelve months, a statistically non-significant amount of bone resorption was reported for both groups.

CONCLUSION: Up to the limitations of this study both treatment options the screw retained and telescopic overdenture can be used for rehabilitation of completely edentulous patients. These cases must be followed for a longer period to have a definite answer regarding their efficiency in the long run.

Introduction

It is well recognised that an edentulous condition has a negative impact on patient's life. Common complaints with conventional dentures are the pain and minimal masticatory efficiency. In combination, these complaints impair function, as well as, lower self-esteem. Recently, Osseointegrated implant-retained prostheses have allowed many patients to improve their quality of life when compared to complete dentures [1-4].

Endosteal implants are the most commonly used. They are manufactured in a variety of widths, lengths, designs and materials [5]. Because of the advantages of the root form implant it is considered the first and most realistic choice on a selection of implant as it offers wide stress distribution with good retention and easy surgical procedure with fairly good healing [6, 7].

Telescopic crowns are also known as a double crown, crown and sleeve coping. These crowns consist of an inner or primary telescopic coping, permanently cemented or screwed to an abutment, and a congruent detachable outer or secondary telescopic crown, rigidly connected to a detachable prosthesis [8, 9].

The screw-retained implant prosthesis consists of artificial teeth connected to a metal frame work with acrylic resin base. By Usually four to five implants are placed in the anterior region to support a cantilevered prosthesis. The length of the cantilever was supposed to be 1.5 times the anterior-posterior span, but shorter in poor quality bone. With moderate to advanced jaw resorption, screw retained prosthesis

can replace lost bone and soft tissue [10, 11]. Also, this prosthesis offers retention security [8]. Up till now, several trials are going on to find a solution for the problem of edentulous alveolar ridge resorption [12]. The trials are devoted to finding a solution by which ridge resorption can be minimised [13-15].

Alveolar ridge resorption is annoying to both the patient and the prosthodontist; Conventional complete denture wearers are in most of the time unsatisfied by their appliances [14, 16]. The advent of dental implants helped to improve the value of the prostheses that may be removable overdenture, fixed prosthesis or fixed detachable appliances [15, 17].

This study was established to evaluate the amount of bone height changes in the posterior mandibular area of edentulous patients receiving screw-retained prostheses versus removable telescopic implant overdentures.

Material and Methods

This study was a clinical trial (RCT), using cone-beam computed tomography (CBCT) imaging and flapless surgical technique to place four implants in the maxillary and mandibular arches utilising tissue supported computer aid ed surgical guides using MIMICS software.

The study was a part of a group study that was performed on fourteen completely edentulous male patients from the outpatient Clinic of Faculty of Oral and Dental Medicine, Cairo University, Department of Removable Prosthodontics. Each patient received eight implants (four in each arch) and was restored with either a telescopic or a screw-retained prosthesis; however, this study was mainly concerned with the mandibular arch as the maxillary arch was the concern of another colleague of the team.

Ethical approval the study protocol was reviewed and approved by staff members of Prosthodontics Department, Ethics Committee, Evidence-based Dentistry committee in Faculty of Oral and Dental Medicine, Cairo University and staff members of Prosthodontics Department, Ethics Committee in National Research Center Egypt.

The patients were selected from the outpatient clinic of the Faculty of the Oral Dental Medicine, Prosthodontics Department, Cairo University according to the following inclusion and exclusion criteria:

Inclusion criteria

Completely edentulous for at least one year, ages range between 50-70 years; adequate bone thickness examined initially by digital palpation, Covered by the adequate zone of keratinized mucosa, Angle's class I maxillo-mandibular relationship.

Exclusion criteria

The presence of any flabby tissue or pathological lesions that may interfere with the surgical procedures or interfere with the proper seating of the prosthesis Patients with systemic disease that may affect dental implants placement andr osseointegration and alveolar bone resorption e.g. Uncontrolled diabetes, hypertension and osteoporosis, neuromuscular disorders [14, 18-22].

Planning was done using specialised software (Mimics 10.01), The obtained DICOM files were imported into it (Fig. 1).

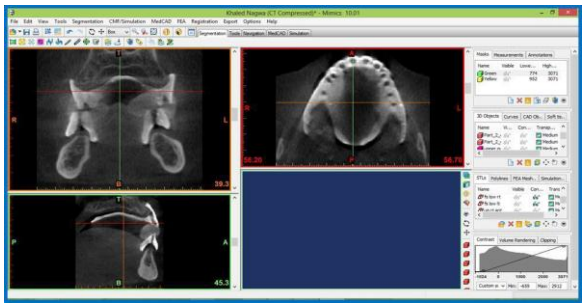

Figure1: Mimics10.01 interface

The proposed implant sites were the canine and the second premolar (bilaterally) (Fig. 2). These proposed sites were identified by the radiolucent channels, previously prepared in the radiographic templates and were evaluated for sufficient bone height and buccolingual width.

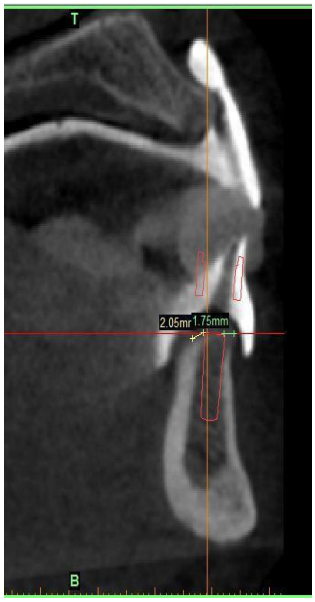

Figure 2: Cross-sectional view showing the distances` measurements around the virtual implants

The proposed implant diameter was 3.75 mm and the proposed length was 10 mm and 12 mm in the posterior and anterior areas respectively. Four virtual implants were placed in each arch, and parallelism between them was checked. Once the positions of implants were accepted in the virtual guide, four holes corresponding to prefabricated metallic sleeves was designed on the MIMICS software.

The virtual implant guide was sent in an STL format to be exported to selective laser sintering (SLS) rapid prototyping machine for guide construction.The sent STL file of the virtual guide was exported into the rapid prototyping machine at the ―Central Metallurgic Research And Developing Institute‖ (CMRDI). The technology used in this study was selective laser sintering [fabricated in a slice-by-slice manner using poly-ether ether-ketone (PEEK)] material. The surgical guide had four holes through which metallic sleeves, with specific dimensions, were fitted through and seated in position, using adhesive [23-26] (Fig. 3).

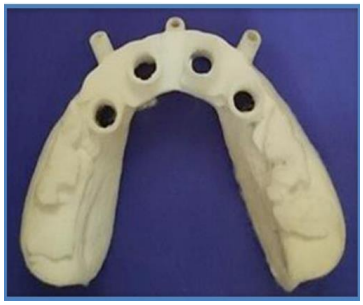

Figure 3: The fabricated surgical guides

A prophylactic dose of 2 gm of amoxicillin and Ibuprofen 600 mg were prescribed for the patient one hour before the surgery [27]. Root formed, tapered threaded dental implants were prepared before surgery. Four implants were prepared with dimensions 3.75 mm diameter and 10 mm and 12 mm length for the canine and premolar area respectively.

After healing period of four months, the surgical stent was used to relocate the position of the implants using tissue punch. Then permanent transmucosal titanium abutments were fastened into the implant fixtures and torqued up to 35 Ncm using torque ratchet.

Acrylic custom trays were constructed on the study casts with a window cut over each implant. Then impression transfer copings were screwed to the abutment using long fixation screws; then open impression technique was used for the final impression making.

Then the patients were grouped into two groups according to a computerized random allocation program. Allocation concealment was ensured as the randomization table was kept with the study coordinator. The 1st[t] Group Screw retained fixed restoration and the 2nd Group Telescopic removable implant overdentures.

Group, I Screw retained fixed restoration

Acrylic resin verification jig was fabricated for passivity check using the single screw test. The prosthesis was screwed intra-orally with a torque wrench. Finally, the access holes were partially plugged with rubber pieces and completely blocked with light-cured composite resin.

Group II Telescopic removable implant overdentures

The obtained cast was sawed to obtain separate removable dies for the analogue with its anti-rotational plastic cap*attached to it; the die was indicated by ditching and the wax pattern of the primary coping was built up in milling wax.

The obtained cast was modified and duplicated into a refractory cast on which the wax pattern of the metallic framework with the secondary copings wea s built up as a mesh work covering the residual ridge and slightly shorter than the acrylic resin denture base. The wax pattern of the framework attached to the patterns of the secondary.

Panoramic radiographs were done immediately after prostheses insertion, six months and twelve months after prostheses use. Panoramic radiography was performed with the Scanora, multimodal radiography system and the screen/ film combination Lanex medium/T-mat G (Eastman Kodak Co., Rochester, N.Y., USA). During the radiographic exposure the patients of the screw-retained prosthesis had their prosthesis fixed in the mouth, however, those of the telescopic crowns wear their conventional acrylic complete dentures after their modification to fit the four implants .the exposure was done while the patients were closing in the centric occlusion.

For calculating the amount of ridge resorption two methods were followed:

I-Mandibular bone height measurement: The radiographs were digitised by scanning, and the following lines were drawn (Fig. 4). (MM`) Horizontal line tangent to the upper border of the mental foramina, (XA)Vertical line tangent to the distal side of the posterior implant of each side to meet the horizontal line at point A. Five and ten millimetres apart of point A two vertical lines were drawn parallel to (XA) till the top of the alveolar bone border. These three vertical lines were measured, and the mean of them was considered during the statistical analysis of this study. The right and left sides mean values were

compared and the degree of bone height resorption was calculated by subtraction: The mean bone height at twelve months the mean bone height at base line and the mean bone height at six months the mean bone height at base line.

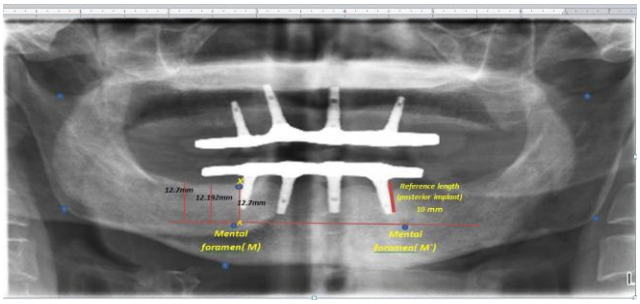

Figure 4: Mandibular bone height measurement

II-Proportional area measurement: This method is similar to that used by Wright et al. 2002 [12] using proportions that minimise errors related to magnification and distortion. The radiographs were digitised by scanning and tracing was done using AutoCAD computer program.

The anatomical landmarks: (Fig. 5) M (lower border of mental foramen), S (sigmoid notch) and G (gonion). These three landmarks were used to construct the triangles on the right side (M-S-G) and left side (M'-S'-G') of the mandible. N (centre of the triangle) (Fig. 6). Center of the triangle If a line was drawn from each corner (or vertex) of a triangle to the midpoint of the opposite sides, then those three lines meet at a centre, or centroid, of the triangle.

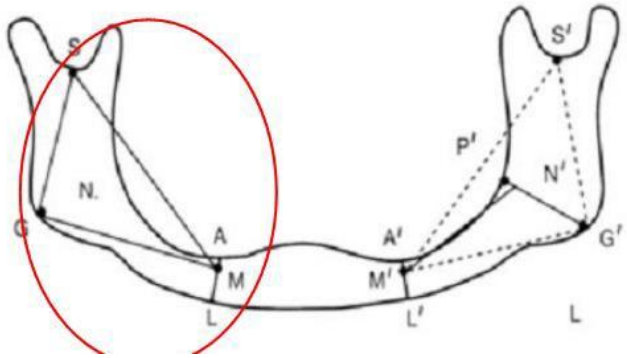

Figure 5: The tracing anatomical landmarks

Boundaries were constructed by the following lines: The boundary line M G, The boundary line A-L; a line from the crest of residual ridge (point A) to the lower border of the mandible (point L) through M perpendicular to M-G, the boundary line M-N and the boundary line G-P; the line G-N extended to the crest of the residual ridge through point P.

The experimental bone area was eventually outlined by the area PAMG and the reference area yof the triangle MGN (Fig. 6). The Posterior Ridge Ratio was calculated by dividing the anatomic bone area (PAMG) by the reference area (MNG), the ratios for the right and left side in each patient were averaged. The change in the posterior mandibular ridge ratio was calculated by subtracting (the ratio at twelve months the ratio at the base line) and subtracting (the ratio at six months the ratio at the base line).

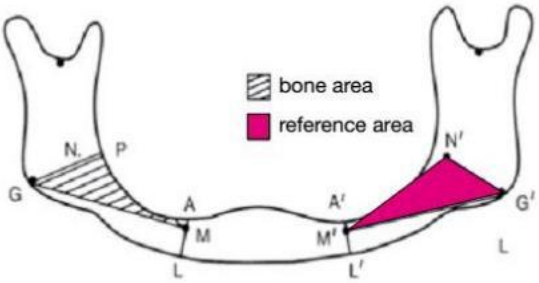

Figure 6: The boundaries of the bone area and reference area

Results

This study started with fourteen patients; however, twelve patients attended the six and twelve months follow-up recall visits after prostheses use. There was a drop out of two patients at both groups one patient has died group II (telescopic overdenture group), and another one was in a group I (screw retained) didn't attend the follow-up appointment. During the different follow-up periods alveolar bone ridge reduction was recorded in both groups but in different degrees. When comparing the mean values of alveolar bone height loss in the right and left sides for each patient in the two groups no statistically significant difference was observed during the different follow-up periods. Therefore the mean values of the decrease of bone height of the right and left sides of the posterior mandibular edentulous ridge were added to represent the mean bone height decrease in each group during the different follow-up periods: Base line (immediately on prostheses` delivery), 1st follow-up (6 months), and 2nd follow-up (12 months).

For the description of the data, the mean values and standard deviations were calculated for proportional areas of the posterior mandibular ridge height at the different three timings and then the changes in posterior ridge height at the different three timings.

For all tests: Data presented as mean and standard deviation (SD) values. Data checked for normality using student t-test, Statistical analysis was performed with IBM® SPSS® (SPSS Inc., IBM Corporation, NY, USA) Statistics Version 23 for Windows.

The mean values and standard deviation of the measurements of the posterior mandibular ridge height were 12.87 ± 2.3 mm, 12.37 ± 2.1mm and 12.31 ± 2.4 mm at baseline, 1st follow-up, and 2nd follow-up respectively. For Group II (Telescopic overdenture): The mean values and standard deviation of the measurements of the posterior mandibular ridge height were 11.78 ± 2.7 mm, 11.71 ± 2.2 mm and 11.68 ± 1.95 mm at baseline, 1st follow-up and 2nd follow up respectively that showed slight higher bone loss in (group I) than (group II) but it remains non-significant (p value>0.05) (Fig. 7).

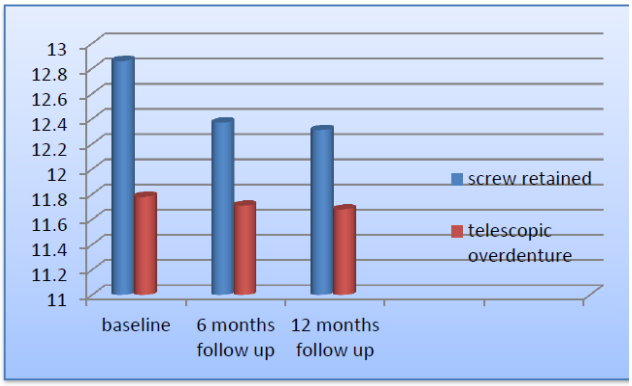

Figure 7: Chart representing the difference between of the measurements of the posterior mandibular ridge height for both groups at the different follow-up periods

The bone height measurements were recorded at baseline, six months and 12 months.The mean bone height loss for Group I Screw retained from base line to the 1st follow-up was 0.33 ± 0.11 mm^2, from 1st follow-up to 2nd follow-up was 0.12 ± 0.09 mm^2 and from baseline to the second follow-up was 0.45 ± 0.12 mm^2. On the other hand, the mean bone height loss for Group II telescopic overdenture was 0.21 ± 0.05 mm^2 from base line to the 1st follow-up, 0.15 ± 0.29 mm^2 from 1st follow-up to 2nd follow-up and 0.36 ± 0.16 mm^2 from baseline to the second follow-up i.e. the bone loss was higher also in group I than in group II but statistically non-significant with (p-value > 0.05) (Fig. 8).

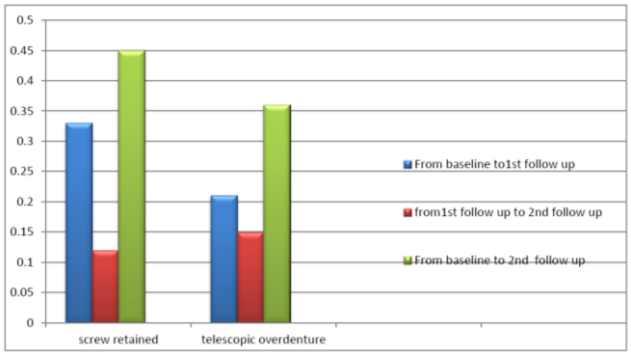

Figure 8: Chart representing comparison between Mean bone height changes for both groups at different follow-up periods

Discussion

In this study, all factors that could affect implant osseointegration, bone height changes and the health of the residual ridge were carefully considered during patient selection and later on after restoration. These factors could be biological or mechanical and most probably both together. The biological factors could be related to the patient's selection, to the design of the implants and tthe steps of implant installation.

On the other hand, the mechanical factors are mainly related to the amount of stress transmitted to the supporting structure whether implants or ridges. Also, the level of oral hygiene is of great importance to the serviceability of the implants and its indirect effect on the residual alveolar ridge changes. The age of the selected patients was nearly the same and ranged between 50 and 60 years to avoid the effect of old age on the degree of bone changes, as the catabolic process is relatively higher than the anabolic process .also hormonal imbalance is another factor. Maintenance of proper oral hygiene may be deficient in old people and hence its effect on alveolar bone changes which is the target of this study. Patients were free from systemic diseases that could affect the metabolic, and a catabolic process weas selected to avoid the adverse effect of systemic disorders on the healing process, a condition of the bone and soft tissues that might affect the results of this study. Regarding the process of brushing in the telescopic group, no difficulty was experienced by the patients as the dentures can be removed and cleaned easily. All patients have been totally edentulous for at least one year before placement of implants to avoid the effect of bone remodelling which follows tooth extraction. Only patients having Angle's class I ridge relationship were selected to avoid subjecting the implants to abnormal forces. The flapless surgical technique was followed in this study due to short surgical procedure causing less damage resulting in less post-operative pain, swelling and discomfort to the patient. The adequate thickness of buccal and lingual bone around the implant was a demand to ensure higher implant stability. Also, safety bone margin of two millimetres from the vital anatomical structures was considered. Cone-beam computed tomography (CBCT) was the imaging technique in this study. Data acquisition was done using Cone-beam computed tomography (CBCT) to visualise bone availability, bone quality and vital anatomical structures. Cone-beam computed tomography(CBCT) allowed visualisation of the bone in a buccolingual direction for optimising the virtual implant placement during the planning phase. Also, cone-beam computed tomography (CBCT) delivers reduced radiation dose and produces a radiographic image of adequate quality to assist in the preoperative surgical planning [28]. The technology used in this study was

selective laser sintering (SLS) rapid prototyping and the material used was polyetheretherketone (PEEK).PEEK provided several advantages like being of high strength; autoclavable possess a high degree of accuracy [26]. Anchoring fixation screws were used to stabilise the template and avoid the rotation during operation [28]. In the screw retained group the parallelism between the implants and passive fit of superstructure is a request in order to avoid the determinant lateral forces that may be applied to the implants, the same principle of passive fit of the appliance was considered in the telescopic group, to assure this in that group primary copings screwed to the implants and secondary copings fixed in the metal framework embedded in the acrylic resin base were precisely done to be passively fit. Also, the metal framework carrying the secondary copings could help this request as it is accurate enough to overcome the discrepancy that could occur if the secondary copings were embedded directly in the acrylic resin.

To assure passive seating of the metallic framework of the screw-retained prosthesis an acrylic resin verification jig was constructed over the implants in the inter foraminal region that must seat passively without movement, rock or interference. In case the jig didn't satisfy this request as happened in one case, the jig was split and screwed to the implant abutment and joined with dura lay inside the patient`s mouth and a new impression was taken. Changes regarding the upper arch are not the concern of this study as it was covered by another member of the team. However, it was opposed with implant prostheses in both groups to simulate to some extent the forces and the stresses transmitted and opposing natural teeth as it was not easy to select all the cases under investigation with single upper dentulous and lower edentulous. Panoramic radiographs have been reported to be sufficiently reliable to evaluate the available bone height in the area of posterior mandible [29]. In this study tracing the panoramic radiograph was done following the proportional method followed by (Wright et al. 2002) [12] during the different follow-up periods. The author considered the changes of the proportional area measurement could represent the changes of the alveolar ridge height. This method helped in studying the changes in a wide area which is not possible with the other means. It is worthy to mention that the examined area is subjected to bone loss due the flexing of the mandible under masticatory load. This can be considered as indirect way of measurement for that reason vertical measurement were done on the radiographs considering the line tangent to the upper border of the two mental foramina as the horizontal base line and the tangent line to last implant on each side as a reference point for vertical measurement, three lines were measured on each side and the mean of them was conceded during the statistical analysis.

Generally speaking, the edentulous alveolar ridge resorption is a continuous process that occurs throughout life, so reduction of the alveolar ridge occurred in the two studied groups is expected. This reduction is most probably due to that the forces transmitted to the ridge exceed the physiological level of tolerance of the alveolar bone. Also wearing of the denture in general changes the ecology of the oral environment which may be responsible for the changes in the supporting soft tissues influencing the state of ridge reduction.

However, this alveolar ridge reduction was not the same in the two studied groups.The reduction was slightly higher in the screw retained group than the telescopic group. Although statistically non-significant this slight difference is most probably attributed to the relatively excessive masticatory forces exerted in the screw retained group as the patients used their prostheses with great confidence as their natural teeth. Another possible factor is the difficulty in maintaining proper denture and oral hygiene as the prosthesis is fixed by screws and patients complained of the difficulty of using brushes, Another point is that isolation of the supporting ridge depriving it of the natural stimulation of food and tongue subjected that tissues to inflammation hence its adverse effect on the degree of alveolar ridge resorption.

On the other hand, regarding the telescopic overdenture group the patient had the chance to maintain good oral and denture hygiene. It also gives ea chance for the tissues to rebound and recoil as the denture was kept out of the mouth during sleeping hours. Also, this group of patients knew that the denture is removable, so they were cautious about using it avoiding eating hard food that needs exertion of that much forces hence the relatively less bone resorption in this group.

Honestly, the results of this study do not recommend one of the two options over the other as the difference in the degree of bone resorption in the two studied groups is very small(statistically not – significant), however, if this study was extended for a longer period the difference might be more evident.

In conclusion, up to the limitations of this study both treatment options the screw retained and telescopic overdenture can be used for rehabilitation of completely edentulous patients. These cases must be followed for a longer period to have a definite answer regarding their efficiency in the long run.

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Development and Psychometric Properties of a Condom Use and Its Cognitive Determinants Questionnaire (CUCDQ)

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Abstract

AIM: The aim of this study was to assess the psychometric properties of Condom Use and its Cognitive Determinants Questionnaire (CUCDQ) among married women in Tabriz, Iran.

MATERIALS AND METHODS: In this cross-sectional study, applying multistage cluster sampling 388 married women were recruited to participate in the study. A comprehensive literature review was conducted to develop CUCDQ. Face, content, and construct validity, as well as reliability, were investigated.

RESULTS: Principal component factor analysis with varimax rotation demonstrated a six factors structure as the best solution [Bartlett's Test of Sphericity (Approx. Chi-Square= 4193.07, df= 780, p<0.001); KMO= 0.815] which explained 43.13% of all the variance between the items. CUCDQ represented a proper validity, reliability, simplicity and functionality.

CONCLUSION: CUCDQ may be helpful for family health care providers and family planning decision makers in precise assessing the behavioural, psychological, and educational factors related to condom use. This scale may be useful in a various range of studies including family planning or STIs prevention studies in different communities. Future research is recommended to assess the different dimensions of the tool in different communities.

Introduction

Family Planning indicators play an important role in balancing the populations' growth to the socioeconomic development of the societies [1, 2]. According to the definition of World Health Organization (WHO), family planning allows individuals and couples to anticipate and attain their desired number of children and the spacing and timing of their births [1].

On the other hand, there is a worldwide estimation of 340 million people newly infected with sexually transmitted infections (STIs) such as HIV [3, 4]. The most of these infections are happened in the poorest regions of the world, as a result of unsafe sex which is known as the second risk factor for illness, disability and death [5].

Considering the lack of vaccines for the most of STIs (especially HIV), condom use has been proposed as one of the most important preventive measures against such infections [6, 7]. If used correctly, a condom may be a reliable method to prevent unplanned pregnancy and many sexually transmitted diseases such as gonorrhoea, chlamydia, trichomoniasis, herpes, HPV, syphilis, chancroid and HIV, as well. As evidence, several previous studies have reported the effect of correct and permanent condom use on reducing the risk of HIV infection by 80% [8-13]. Moreover, based on the statistics reported by WHO, the failure rate of a condom, in perfect use, to prevent pregnancy is about 2% [14, 15].

Although the cost-effectiveness of condom use as a relatively simple intervention to prevent STIs have been, well, documented in previous studies [16, 17], condom effectiveness may be affected by people errors and inconsistent use [18]. The common errors

resulting in reduction in the effectiveness of condom use are incomplete use (like applying the condom only before orgasm and/or early removal of the condom before orgasm), not leaving space at the tip, not squeezing air from the tip before use, not using water-based lubricants and incorrect withdrawal [15].

Despite the remarkable role of condom use in STIs prevention, few studies have been conducted on this behaviour and its contributing factors in Iran. Fallahi et al., [19] in a study of people living with HIV/AIDS, suggested to study the associated factors of STIs (condom use) among the Iranian population. On the other hand, accurate research on a subject with the least mistakes needs reliable and validated instruments related to the subject [20]. To our knowledge, there is no valid, reliable and Iranian-native instrument for condom use and its cognitive factors in Iran. Therefore, the aim of this study was to develop an instrument named as Condom Use and its Cognitive Determinants Questionnaire (CUCDQ) and to assess its psychometric properties. Such instruments may help investigators in precise assessing the behavioural, psychological, and educational factors related to condom use, aiming to address the issue in a various range of studies including family planning or STIs prevention studies in different communities.

Material and Methods

Participants

In this cross-sectional study, applying multistage cluster sampling 388 housewives in Tabriz, Iran, were recruited to participate in the study. There are ten urban regions in Tabriz. To recruit the respondents, two healthcare centres were randomly selected from each region (20 centres). Then, based on the health documents of the population in the health care centres, 22 married women, who used the condom as a contraceptive method, were randomly invited to complete the questionnaires (Response Rate = 88%).

The inclusion criteria included the 15-49 years old married women who used the condom as a contraceptive method and were consent to participate in the study. The exclusion criteria were those women who announced no intercourse with their partner in the previous year, were not in the range of 15-49 years of age and refused to participate in a study.

Ethical approval for the study was provided by Ethics Committee in Tabriz University of Medical Sciences (Ethics Code = 5.4.98341). Before providing the participants with the questionnaires, the purpose of the study was explained and all those accepted the participation signed a consent form.

Instrumentation

The data were collected by a researcher-made questionnaire. To design the instrument a comprehensive literature review [19, 21-24] was conducted to provide an item pool focusing condom use behaviour and its cognitive factors. In this stage, all the possible contents related to the target constructs and the most relevant items to the cognitive factors associated with condom use were systematically selected. One of the researchers cross-checked the derived items. Finally, 50 items were selected.

A panel of experts, including four scholars in the areas of health education and behaviour, a psychologist and a midwife with a field experience in maternal health and family planning reviewed and assessed the items and evaluated the relevance and appropriateness of the items to the married women. The panel, also, evaluated the response format of the scale and confirmed the items to be representative of the constructs. In this stage, four items were omitted considering the suggestions of the expert panel. The instruments were revised based on the feedback from the panel of experts which was mostly regarding the wording and phrasing of the items. The first draft including 46 items was prepared following consultation with the multidisciplinary team. A brief description of the instruments follows.

The initial instrument (50 items) was categorized into six scales, based on the nature of the items, including Knowledge on Condom Use Scale (KCUC), Attitude Toward Condom Use Scale (ACUC), Barriers of Condom Use Scale (BCUC), Errors in Condom Use Scale (ECUC), Willingness to Condom Use Scale (WCUC) and, Behavioral Pattern of Condom Use Scale (BPCUS).

KCUC measured the individuals' awareness and understanding on how to use the condom. This scale included 8 items with 3-point responses (yes = 2, no = 0, I don’t know = 1). Examples for KCUC are *Condom should be drawn to the bottom of the penis* and *Condoms should be used before any contact between penis and vagina*. The possible score for this scale ranged from zero to 16. The higher total score for a respondent indicated higher knowledge about condom use.

ACUC was a ten-item scale that was developed to measure the attitudes towards condom use by asking the women about their level of agreement. A five-point Likert-type scaling was used (one = totally agree, two = agree, three = no idea, four = disagree and five = totally disagree). Examples of the items are *Using condom destroys my sexual appeal*, and *Using condom is unfair as it decreases sexual pleasure*. After recoding the negatively stated items, the theoretical range was 0–50, in which higher scores indicate more positive attitude.

BCUC included 7 items with 3-point scaling

(yes = 2, no = 0, I don't know = 1). The scale assessed the beliefs of the respondents on the barriers to using condom. Two examples of the items are as follow: *The erection of my husband goes away before wearing the condom* and *Condom slips while ejecting penis from a vagina, at the end of intercourse*. The theoretical range for this scale was 0-14. The higher total score indicated more perceived barriers of condom use.

ECUC consisted eight items with three possible answers (yes = 2, no = 0, I don't know = 1) which measured the common errors of condom use during intercourse. Examples of the items are *the used condoms may be reused again*, and *a sharp object should be used to open the condom package*. The possible score for this scale ranged from zero to 16, higher the score, the higher rate of errors while condom use.

WCUC was a 7-item scale with 3-point scaling (yes = 2, no = 0, I don't know = 1) that measured the level of willingness among the women to use the condom. Two examples of the items included: *I feel worries while using the condom during intercourse* and *My husband is reluctant to use the condom*. Theoretical range for this scale was 0-14. The higher score indicated more willingness to use condom among the respondents.

BPCUS comprised ten items. In this scale, the women were asked to report the behavioural patterns of using the condom on a regular basis (once a month) during the previous 12 months. The women should select Yes or No for each item, which resulted in a theoretical range of zero to 10. The higher scores represented, the more appropriate pattern of condom use behaviour among the women.

Along with the instrument, a Demographic Data Form was also provided to the respondents. The demographic characteristics included ten variables as follow: age, level of education, occupation, age at menarche, age at marriage, the number of pregnancies, the number of children, and the desired number of children.

To provide the pre-final version of the scales, content and face validity were performed. The Content Validity Index (CVI) and Content Validity Ratio (CVR) were used to validate the content of the instrument, quantitatively.

To determine the CVR, the abovementioned expert panel members were asked to consider the necessity of each item by a 3-point Likert-type scale (It is necessary, It is useful but not necessary, It is not necessary). Items with the value more than 0.62 (based on the Lawshe table), were considered as necessary for the instrument [25]. To determine the CVI [26], the expert panel was, also, asked to assess the relevancy, clarity, and simplicity of each item. These three criteria were analysed, separately, by a 4-point Likert-type scale. Those items with the CVI value less than 0.75 (2 items), were considered as inappropriate [27] and, therefore, deleted from the questionnaire.

Face validity of the instruments was carried out with both quantitative and qualitative methods. The same expert panel evaluated the quality of each item for difficulty, relevancy and ambiguity. To quantify the face validity of the items, the importance of each item was scored based on a 4-point rating scale. The impact of each item was calculated by multiplying the frequency of an item by its mean importance [Impact Score = Frequency (%) × importance]. The impact score for the items was considered to be 1.5 or higher, as recommended, previously [28]. Eventually, 1 item was removed, and the CUCDQ including 43 items was produced.

The reliability of the questionnaire was assessed using the Cronbach's alpha coefficient. Moreover, the test–retest reliability coefficient was conducted. The questionnaires were completed, on a second occasion, by 20 randomly selected women similar to the study participants, two-weeks later. The Intra-class correlation coefficients (ICC) with 95% confidence intervals (CI) were calculated, and those items with an ICC equal to or more than 0.70 were considered as acceptable.

Statistics

Data were analysed using the $SPSS_{21}$ statistical software package (SPSS Inc., Chicago, IL, USA). Central tendency and variability measures were used to summarise and organise the data. Content Validity Index (CVI) and Content Validity Ratio (CVR) were applied to assess the content validity. Exploratory Factor Analysis (EFA) was utilised to determine the construct validity and factor structure of the instrument. Also, the internal consistency of the instrument was assessed applying Cronbach's alpha coefficient method. ICC was, also, used to calculate the test–retest reliability coefficient. Descriptive (frequency, mean, standard deviation) and inferential statistics (Pearson correlation coefficient, and linear regression) were used to answer the research questions. P value less than 0.05 was considered statistically significant.

Results

The mean age of the participants was 30.77 ± 6.32 years. About 23% of the women had a less than diploma level of education. The majority of the participants (71.9%) were the employee. The demographic characteristics of the women participated in the study as well as the relationships between the characteristics and the mean score of the factors are shown in Table 1.

Table 1: Relationship between the respondents' characteristics and the mean score of the factors

Variables		Frequency (%)	1 p	2 p	3 p	4 p	5 p	6 p
Age (yrs.) (n = 394)	15-28	154 (38.9)	0.258	0.078	0.240	0.220	0.186	0.093
	28-37	196 (49.5)						
	38-47	37 (9.3)						
	48-49	7 (1.8)						
Age of husband (yrs.) (n = 395)	Younger than 28	50 (12.5)	0.354	0.115	0.276	0.919	0.127	0.479
	28-37	252 (63.6)						
	38-47	77 (19.4)						
	48 and older	16 (4)						
Age at the monarch (yrs.) (n = 360)	9-12	75 (18.9)	0.008	0.045	0.739	0.222	0.144	0.147
	13-14	209 (52.8)						
	15-17	76 (19.2)						
Age at Marriage (yrs.) (n = 393)	Younger than 17	38 (9.6)	0.693	0.099	0.670	0.259	0.834	0.872
	18-22	173 (43.7)						
	23-27	130 (32.8)						
	28-32	44 (11.1)						
	Older than 32	8 (2)						
Occupation (n = 392)	Housewife	110 (27.8)	0.004	0.647	0.927	0.335	0.548	0.982
	Employee*	280 (70.7)						
	Other	2 (0.5)						
Occupation of husband	Employee*	120 (30.3)	0.952	0.198	0.878	0.409	0.569	0.984
	Self-employed	240 (60.3)						
	Other	34 (8.6)						
Level of Education (n = 393)	Under Diploma	91 (23)	0.197	0.002	0.47	0.316	0.316	0.017
	Diploma	144 (36.4)						
	Higher education	158 (39.9)						
Level of Education for husband (n = 394)	Under Diploma	104 (26.3)	0.273	0.035	0.677	0.011	0.131	0.333
	Diploma	131 (33.1)						
	Higher education	159 (40.2)						
Number of pregnancies (n = 395)	1-2	44 (11.1)	0.051	0.884	0.544	0.694	0.585	0.889
	3-5	313 (79)						
	6 and more	38 (9.6)						
Number of children (n = 396)	0	50 (12.6)	0.136	0.641	0.474	0.961	0.858	0.276
	1	211 (53.3)						
	2-3	121 (30.6)						
	4 and more	13 (3.3)						
Number of desired children (n = 376)	0	41 (10.4)	0.091	0.460	0.460	0.496	0.103	0.679
	1	171 (43.2)						
	2-3	145 (36.6)						
	4 and more	19 (4.8)						

Factor 1 = Negative Attitude toward Condom Use (NACU); Factor 2 = Behavioral Pattern of Condom Use (BPCU); Factor 3 = Perceived Barriers of Condom Use (PBCU); Factor 4 = Errors in Condom Use (ECU); Factor 5 = Willingness to Condom Use (WCU) and Factor 6 = Knowledge on Condom Use (KCU).

Construct validity

EFA was conducted applying the principal component factor analysis with varimax rotation. Bartlett's Test of Sphericity (Approx. Chi-Square = 4193.07, df = 780, $p < 0.001$) and Kaiser-Meyer-Olkin (KMO) measure (KMO = 0.815) showed suitable correlation matrix and sampling adequacy, respectively, for factor analysis.

Six factors extracted with eigenvalues more than 1, of which, 43.13% of all the variance between the items were explained. The rotated factor pattern coefficient for variables solution is shown in Table 2. For each factor, information is provided regarding the initial eigenvalues (before rotation), variance accounted for after rotation (rotation sum of squares), percentage of the variance explained (after rotation), intra-class correlation coefficients (ICC) with 95% confidence intervals (CI) and internal consistency reliability as showed by Cronbach's alpha for each factor.

As it is shown in Table 2, one of the six factors had Cronbach's alpha less than 0.6, which argues omitting of this factor. The simple structure and the best solution were determined considering visual inspection and the hyper plane count [29], respectively, and the authors decided not to remove the factor's items. Thus, this factor pattern considered as the optimal solution. The factor pattern coefficient values were used to interpret the factors. According to the recommendations noted by Gorsuch [29] and Tabachnick and Fidell [30], the cut-off of 0.40 was considered to include one item in the interpretation of a factor (Table 2). Factors were named as follow: 1 = Negative Attitude Toward Condom Use (NACU); 2 = Behavioral Pattern of Condom Use (BPCU); 3 = Perceived Barriers of Condom Use (PBCU); 4 = Errors in Condom Use (ECU); Willingness to Condom Use (WCU) and Knowledge on Condom Use (KCU).

Table 2: Rotated matrix of the items of Condom Use and its Cognitive Determinants Questionnaire

Items	Factors*					
	1	2	3	4	5	6
Using condom destroys my sexual appeal	.841					
Using condom makes sexual relationship non-enjoyable	.831					
Using condom decreases my sex pleasure	.817					
Condom Use is annoying	.745					
I don't like using condom	.736				-.217	
Using condom is unfair as it decrease sexual pleasure	.632	.253				
The man who uses condom express concern and dissatisfaction with sexual relationship to his partner	.446	.284				
I do not want to use condom as it cause allergy to me	-.396				.353	
If my partner proposes condom use to me, it means that he doesn't trust me	.389					
I avoid using condom as far as possible	.360					
Condom may slip at the beginning of intercourse		.770				
The erection of my husband goes away before wearing the condom		.664		.327		
Condom slips during intercourse		.649				
Condom slips while ejecting penis from vagina, at the end of intercourse		.637				
The erection of my husband goes away after wearing condom and at the beginning of intercourse	.230	.513				
Condom does not fit the penis of my husband, and I can feel it during intercourse		.454		.332		
Condom is perforated during intercourse		.447		.347		
When I feel risk for pregnancy/infection during a sexual relationship I use a condom			.682			
During my ovulation period (the tenth to the eighteenth days) I use condom			.679			
I use condom to prevent sexually transmitted diseases and AIDS			.663			
In the case of failure in our routine contraceptive method, We use condom			.650			
My husband use condom only before ejaculation			.551			
We use condom throughout our intercourse			.474		.208	
My husband wear condom before erection			.420			
The used condoms may be reused again				.769		
The timely expired condoms may be used				.719		
A sharp object should be used to open the condom package				.626		
A condom may be reused for several times			.287	.442		
There is no need to check the condom regarding perforation and defection				.397		
Using condom is difficult					.728	
I feel worries while using condom during intercourse					.694	
My husband is reluctant to use condom		-.234			.442	
I have no confidence to use condom as a contraceptive method					.431	
My husband does not appropriately cooperate in using condom while intercourse	-.268	-.326			.421	
The used condoms shouldn't be reused						.703
The perforated or defected condoms shouldn't be used						.665
The Latex condoms should be used			.242			.441
Condom should be drawn to the bottom of the penis					.212	.397
Condom should be drawn on an erected penis						.384
Condoms should be used before any contact between penis and vagina			.266		.247	.332
Initial Eigenvalues	6.68	3.09	2.41	1.84	1.65	1.56
Rotation sums of squares	4.85	3.16	2.85	2.56	2.24	2.01
Percent of variance explained	16.70	7.72	6.02	4.62	4.13	3.91
Cronbach α	0.77	0.79	0.70	0.65	0.61	0.51

Factor 1 = Negative Attitude Toward Condom Use (NACU); Factor 2 = Perceived Barriers of Condom Use (PBCU); Factor 3 = Behavioral Pattern of Condom Use (BPCU); Factor 4 = Errors in Condom Use (ECU); Factor 5 = Willingness to Condom Use (WCU) and Factor 6 = Knowledge on Condom Use (KCU). * In order to help in decreasing complexity of the table, the loadings less than .2 were omitted.

The bivariate correlation coefficients between the factors are shown in Table 3. Statistically, significant correlations were found between factors 4 (ECU) and all the other factors, except for factors number 3 and 6. The highest and the lowest significant correlations were found between the factor 1 and 2 (r = 0.414) and the factor 3 and 4 (r = -0.141), respectively.

Table 3: CUCDQ factors Correlation Matrix

Factor	1	2	3	4	5	6
1	1					
2	0.414*	1				
3	-0.032	0.048	1			
4	0.174*	0.381*	0.141*	1		
5	-0.408	-0.276*	-0.015	-.211*	1	
6	-0.087	-0.069	0.169*	-0.083	0.092	1

Factor 1 = Negative Attitude toward Condom Use (NACU); Factor 2 = Perceived Barriers of Condom Use (PBCU); Factor 3 = Behavioral Pattern of Condom Use (BPCU); Factor 4 = Errors in Condom Use (ECU); Factor 5 = Willingness to Condom Use (WCU) and Factor 6 = Knowledge on Condom Use (KCU). * $p < 0.05$.

Discussion

If used correctly and permanently, condom use is among the safest ways to prevent unintended pregnancy and sexually transmitted diseases (STDs), as it has no side effect-unlike the most of other methods of contraception [8]. However, the effectiveness of this contraceptive method may be reduced due to various causes and factors. The most of the previous studies have focused on the physical causes of the condom use failure [31, 32], and few studies have examined the cognitive factors of the issue. A reason may be the lack of valid and reliable instruments designed specifically, to assess the condom use cognitive factors. Hence, the purpose of this study was to assess the psychometric properties of CUCDQ among Iranian women, to provide a background and a standard tool for further research on identifying the cognitive factors associated condom use.

Exploratory factor analysis showed a six factors structure as the best solution for the instrument. The factors named as Negative Attitude Toward Condom Use (NACU), Perceived Barriers of Condom Use (PBCU), Behavioral Pattern of Condom Use (BPCU), Errors in Condom Use (ECU), Unwillingness to Condom Use (UCU) and Knowledge on Condom Use (KCU). This solution predicted 43.13% of the total variance among the items, within which the explanatory power of the first three factors was 30.45%.

The results showed a moderate to high internal consistency for the factors of CUCDQ, according to the reference table provided by DeVellis [33] as well as Sim and Wright [34]. Cronbach's alpha for the factors was ranged between 0.51 and 0.79. In consistent with the present study, internal consistency was applied in several previous studies [35-41] to confirm the reliability of different questionnaires. Moreover, applying face and content validity as well as measuring the CVI, the simplicity, clarity and relevancy of the instrument were assured.

Previous studies have suggested that correlations among factors should be reported [29, 35], as it may help other researchers to compare the results. Also, Gorsuch [29] recommended that the correlation between a factor and its related factors may be used as Cronbach's alpha coefficient to demonstrate the stability of each factor. The correlation between the CUCDQ factors indicated a range of low values (at least, -0.015 between NACU and BPCU) to average values (the highest, 0.414 between NACU and PBCU).

Based on the findings, there was a significant positive relationship between factors 1 (Negative Attitude Toward Condom Use) and 2 (Perceived Barriers of Condom Use), which means that more negative attitude toward condom use may result in more perceived barriers to using it. Also, in the present study, a significant negative correlation was found between factors 4 (Errors in Condom Use) and 5 (Willingness to Condom Use), which suggests that increasing the level of willingness to use condom associates to decreasing the level of common errors in the behaviour. Trussel and Guthrie [42] also suggested that common errors in condom use may lead to the failure of this contraceptive method and ultimately change the attitudes of people towards it as a contraceptive method.

There was also a significant positive correlation between factors 4 (Errors in Condom Use) and 3 (Perceived Barriers of Condom Use). Sanders et al., [15] found similar results and reported that condom use errors, such as using it before sex might be a barrier to use it among couples.

In general, condom use is an interpersonal behaviour, which may be affected by several psychosocial factors. As an emphasis, Warner et al., [43] concluded that the use of condom, despite the seemingly simple features (such as low cost and non-prescription availability), is a multi-faceted performance, which, even in the best conditions, is influenced by factors like inexperience, previous negative experiences in performing the behavior and gender inequalities in social relations. He also, emphasised that the use of the condom may be inherently more complex and more difficult due to such influential factors.

As limitations of this study, the low Cronbach's alpha coefficient in some factors and the weak to moderate correlations between the factors may be noted. These weaknesses may be due to the low number of sample. Considering the number of items (43 items), we invited 440 women in the study. But, as condom use and its associated cognitive factors are a taboo to be spoken about in Iranian

culture, about 12% denied to participate in the study. In the case of studying such culture-sensitive subjects in Islamic countries, the higher number of sample size is recommended to compensate the sample use. Moreover, due to the high privacy of the subject, some of the women may not answer to the items accurately. Therefore, providing greater accuracy in data collection of future studies among less open communities is recommended.

In conclusion, CUCDQ was found to be, appropriately, valid, reliable, simple and practical in the present study. Therefore, this instrument may be used as a useful instrument to assess condom use and its cognitive associates among Persian language communities. CUCDQ may help family health care providers and family planning decision makers in precise assessing the behavioural, psychological, and educational factors related to condom use, aiming to address the issue in a various range of studies including family planning or STIs prevention studies in different communities. Future research is recommended to assess the different dimensions of the tool in different communities and also to compare the dimensions with the other indicators of family planning and STIs prevention.

Author Contributions

HA, AT and SK were involved in the conception of the study, performed the analyses and drafted the manuscript. HN and TB were involved in the conception of the study, interpreted the results from the analyses, and HN assisted in drafting and revising the manuscript.

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Public Health

Effect of Sanitary-Environmental Conditions of Diabetic Hypertension Incidence in Displaced Persons

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Abbreviations: BMI = body mass index; CHD = coronary heart diseases; CVD = cardio-vascular diseases; FRY = Former Republic of Yugoslavia; MBG = mean blood glucose; PTSD = post-traumatic stress disease; WHR = waist/hip ratio.

Abstract

BACKGROUND: The abnormal conditions of life and genetic factors often play a major role in the incidence of "diabetes - diabetes", heart disease and vascular disease, jaundice and posttraumatic stress.

AIM: Trauma and posttraumatic stress are most common in the displaced persons, and the focus of this paper is to focus on this issue regarding cases in former Yugoslavia, and now in our country. These diseases are caused by increased beta-cell sensitivity to viruses, the development of autoimmune antibodies attacking their pancreas cells, degenerative changes in cells that result in the change of structure and of insulin production.

MATERIALS AND METHODS: In this paper, we have taken into account the traumatic events and long-term psychosocial consequences for internally displaced persons, several years after displacement, and found a high level of PTSD symptoms.

RESULTS: This stress is present in almost 1/3 of internally displaced persons, and every sixth person has suffered from PTSD in the past. Respondents suffer from symptoms of intrusion, but there was a large number of symptoms, such as avoidance and increased arousal. We also found that gender, age and education are related to the symptoms.

CONCLUSION: Females, and older respondents and internally displaced persons with lower levels of education show a higher level of PTSD symptoms.

Introduction

Diabetes mellitus or diabetes (diabetes mellitus, διαβήτης) is a chronic, incurable systemic disorder of metabolism, which manifests itself as hyperglycemia and permanently elevated level of blood glucose. It is mainly caused by hereditary factors, and it is usually the result of reduced secretion or reduced biological effects of the hormone insulin, but it could also be the result of the combination of these two factors. This deficiency impedes the exchange of carbohydrates, fats and proteins in the body (which is the common symptom of the issue), and after a longer period, it influences the structure and function of blood vessels, nerves, and other vital organs [1-5].

Jaundice denotes yellowish tissue disease, which manifests itself as a yellowing of the skin and deep tissues. The most common cause of hepatitis is a large amount of free or conjugated bilirubin in the extracellular fluids. The normal bilirubin concentration in plasma (free-form) is on average of 9 mmol/l. In the certain pathological conditions, the concentration of bilirubin can be increased to 700 mmol/l. In the case of obstructive jaundice, caused either by an obstruction of the bile ducts, or by damage to the liver cells, the creation of bilirubin is normal, but the

bilirubin created cannot reach the intestine from the blood. Free bilirubin further enters liver cells wherein it conjugates in a usual manner and creates problems for the body.

Trauma and posttraumatic stress among IDPs are results of numerous wars in the previous Yugoslavia, Yugoslavia and after the secession of the former federate republics, and to this day there have been more than one million refugees in the area.

Diseases of the heart and blood vessels are also frequent complications following all forms of diabetes, and one of them is gangrene of the feet and so on. Hypertension is a major risk factor for chronic cardiovascular and cerebra-vascular diseases, which are particularly noticeable among internally displaced persons above all due to degraded living conditions [6, 7].

Diseases of Diabetic Hypertension

The word diabetes was first used by Demetrius of Apollonius around 200 BC. It is derived from the Greek word διαβαίνειν which mean "flow through", corresponding to one of the main symptoms of the disease - constant fluid intake and excessive production of urine (urine).

In 1675, Thomas Willis added, to the name of the disease, the word Mellitus, which was derived from Latin and means "sweet" (this is connected to the sweet taste of urine of the affected individuals). Matthew Dobson proved in 1776 that the sweet taste comes from the presence of sugar in the blood and urine of the diabetics [8, 9].

Despite the fact that it was known about for a relatively long time, diabetes was first experimentally determined and described at the end of the nineteenth century. Discovery of the role and importance of pancreas in the development of diabetes has been attributed to the scientists Joseph von Mering and Oskar Minkowski. In 1889, they discovered that dogs with removed pancreas soon started manifesting all the signs and symptoms of diabetes, and they died shortly after that. In 1910, Sir Edward Albert Sharpey suggested that people with diabetes lack one of the substances produced by the pancreas, and he proposed to call it insulin. The name is derived from the Latin word insula, which means "island", referring to the fact that insulin creates beta cells of the islets of Langerhans in the pancreas [10].

The endocrine role of the pancreas in the metabolism, as well as the actual discovery of insulin, were not defined until 1921 when Ser Frederick Grant Banting and Charles Best Herbert demonstrated that in dogs without the pancreas, diabetes can be prevented by administering the extract of the islets of Langerhans of healthy dogs. Banting, Best and colleagues (especially the chemist Kolip) were able to isolate insulin from the pancreas of cattle at the University of Toronto, and in 1922, its use was allowed in the treatment of diabetes. A year later, Banting and laboratory director MacLeod won the Nobel Prize for this discovery [11]. They were protected from a patent disclosure but allowed its use without compensation, which contributed to the rapid expansion of the application of insulin in the treatment of this disease worldwide [12].

The difference between type one diabetes and type two was first discovered and published by Sir Harold Percival Himsworth in January 1936 [13].

According to WHO (World Health Organization), etiological classification of diabetes includes [14]:

- Type 1 diabetes - occurs when the pancreas produces too little insulin or cannot produce it any more. This disorder usually occurs suddenly in childhood or adolescence.
- Type 2 diabetes - is the most common form of diabetes. In this disorder, the pancreas continues to secrete insulin, but the cells of the body become resistant to its effects. This type of diabetes affects people over the age of 40 and often affects obese people.
- Gestational diabetes usually occurs after giving birth; however, women who are afflicted by it have a higher chance of developing type 2 diabetes later in life.

Experiment

Trauma and post-traumatic stress are vicious diseases among IDPs, and they are the result of numerous wars in the previous Yugoslavia, FRY as well as in the succeeding states. From 1991, until today in this area, there are over 1 million refugees, although not all of them responded to the last census. Revision of their refugee status is in progress, and it is expected that about 30% of them would lose that status due to the acquisition of citizenship, the appliance for a program of return to the former republics and now separate states or because they did not respond to the census. Experimental research will be in compliance with the Helsinki Declaration.

The bad economy and unstable political situation hamper the integration of refugees, which is the permanent solution chosen by 60% of the refugees. Inadequate housing and high unemployment are the two main problems of the refugees and displaced persons. The inability of finishing works on the residential units without help, the problem of legalization, poor infrastructure, the inability to obtain grants and loans (only about 20% of refugees have somehow solved their housing problems), the inability to be properly informed and lack of education in self-employment opportunities, failure in take part in the labor market also contribute to the issue of integration.

Risk factors for coronary disease

The term "risk factor" is often used to describe features found in healthy individuals and which have been determined by epidemiological studies to be associated with the subsequent occurrence of the disease, in this case of CHD.

In the elementary sense, the term risk factors include changeable and immutable characteristics of each. NIDDM is a significant risk factor for the development of cardio-vascular diseases (CVD) in both men and women. Data obtained from the studies indicate that the risk of cardiovascular disease is 2 to 4 times higher in NIDDM patients than in non-diabetics and that the annual rate of fatal and non-fatal cardiovascular disease occurrence in NIDDM patients is 2 to 5%.

To verify this data, and, to determine the presence and importance of risk factors for coronary heart disease in diabetics, we examined 60 insulin dependent diabetes patients treated at a health centre.

All patients had clinically proven non-insulin dependent diabetes, and according to the presence of coronary disease were divided into two groups: Group I-NIDDM patients with coronary disease; Group II-NIDDM patients without coronary disease. In addition to taking a detailed medical history, the following data were measured: body mass index (BMI) and waist/hip ratio (WHR), which were evaluated based on the criteria of European NIDDM Policy Group (1996) [15].

From biochemical parameters which are risk factors for CHD, acidum uricum and fibrinogen were determined. The level of risk assessment for coronary disease was performed according to the criteria of the European Association for atherosclerosis - EAS where the table was determined by a ten-year absolute risk assessment. Statistical analysis was performed using methods of descriptive and analytical statistics in Excel 7.0 and Windows 98 environment, and the results have been shown in the table and diagram.

The following was performed: the measurement of blood pressure; determination of fasting plasma glucose and daily glucose profile. From morning venous blood samples total cholesterol (HOL), HDL cholesterol, triglycerides (TG), and LDL cholesterol was determined.

Results

Out of a total number, 37 patients (62%) were female, and 23 (38%) were males. The average age of the patients was 57.98 ± 7.3 years, whereas there was no significant difference in age between men and women 58.8 ± 9.3 vs. 57.5 ± 7.23 years prospectively. Duration of diabetes was significantly higher in women than in men 9.2 ± 6.71 vs. 6.12 ± 7.13 years (p <0.05).

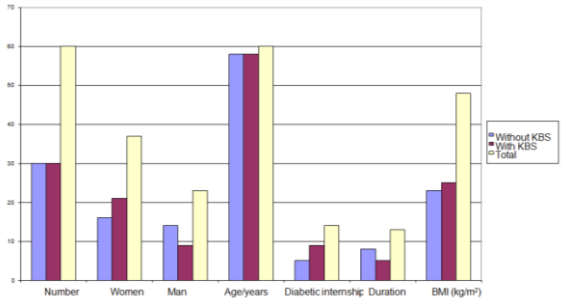

Figure 1: The characteristics of the studied patients

Although there were no significant differences in glycemic control, the value of daily mean blood glucose profiles (MBG), was much higher in treated patients 9.97 ± 3.29 mmol/l Waist/hip ratio (WHR) was significantly higher in male patients than 0.92 ± 0.04 vs. 0.87 ± 0.03 in females ($p < 0.01$), as the finding expected. The degree of obesity expressed in body mass index (BMI) showed significantly higher values in women than in men 29.75 ± 4.48 vs. 27.46 ± 2.74 kg/m^2 ($p < 0.01$), while the average value of this parameter in the study group was 28.86 ± 3.95 kg/m^2 above the WHO recommendation.

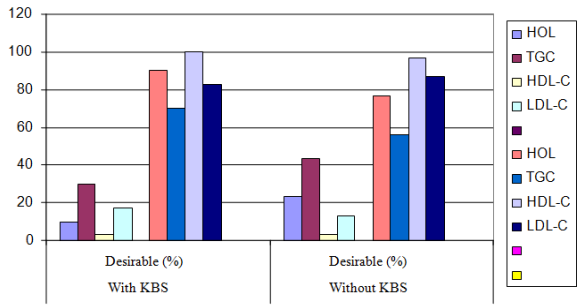

Figure 2: The prevalence of lipid disorders

Coronary heart disease was significantly more prevalent in women than in men 21 (70 %) vs. 9 (30 %) ($\chi 2 = 8.06$, $p < 0.01$). The intensity of the connection between gender and the occurrence of CHD in diabetics was examined by test contingency. Test results unambiguously showed an extremely high degree of correlation between the appearance of CHD and females in diabetics ($C_{max} = 0.707$, $C = 0.61$).

Basic characteristics of patients with CHD and without CHD are shown in Figure 1 the mean age of diabetic patients was 57.9 ± 7.3 years. There was no significant difference between the groups with KBS and without KBS. The diabetic length of service was 8 ± 7.1 years, and the duration of dyslipidemia 5.7 ± 4.72, whereas there was no significant difference between the groups. BMI values were significantly higher in patients with CHD compared to diabetics without CHD 29.77 ± 3.55 vs. kg/m^2 27.97 ± 3.95 (p <

0.05).

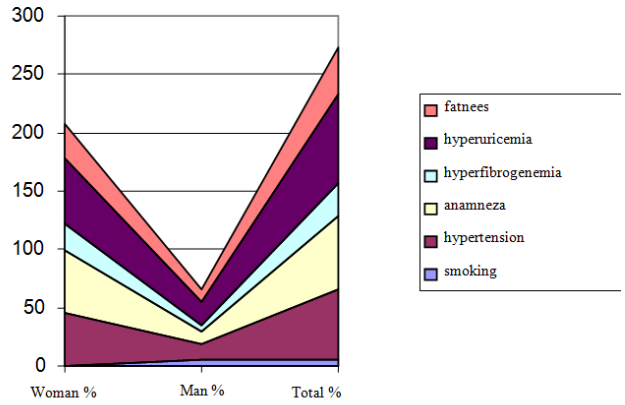

Figure 3: Representation of non-lipid risk factors in patients with CHD

Elevated lipid risk levels (high-risk + border) for cholesterol (HOL) had 90% of patients with CHD and 76% without CHD, which proved to be statistically significant ($\chi 2 = 6.12$, $p < 0.05$). A significantly higher percentage of patients in the group with CHD had elevated lipid levels and risk for triglyceride (TG) 70% compared to patients without CHD, 56.5% ($\chi 2 = 4.36$, $p < 0.05$). Other parameters did not show significant differences in the distribution between the two groups. Representation of non-lipids risk factors for CHD is shown in Figure 4. It is evident that some non-lipid risk factors were present at high levels in the observed group of diabetes patients with CHD. Hypertension, as a risk factor was present in 60% of patients and a positive family history for the existence of a cardiovascular disease, was present in 63% of patients. Obesity is defined as BMI > 30 kg/m^2 and was found in 40% of the patients. The possible existence of the improper distribution of non-lipids risk factors according to gender was investigated by Fisher's exact test of probability. The test showed a significant difference in the occurrence of smoking regarding gender (0% women vs. 6% of men, $p < 0.05$) and in a positive family history (53% women vs. males 10%, $p < 0.05$).

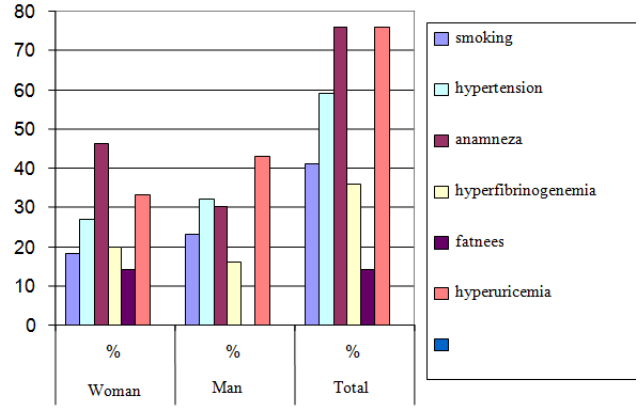

Figure 4: Representation of non-lipid risk factors in patients without CHD

It is evident, judging by the table, that some non-lipid risk factors were present at high levels in NIDDM diabetics without CHD. Hypertension as a risk factor is present (similar group, 60%) in 59% of patients. A family history of the cardiovascular disease was found in 76% of patients.

Obesity is defined as BMI > 30 kg/m^2 and was found with a small percentage of patients: 13.6%, in contrast to the diabetes patients with CHD which was present with 40% of patients. Smoking unexpectedly exhibited a high level of incidence of 4% in one group of patients (current smokers and abstainers in less than two years).

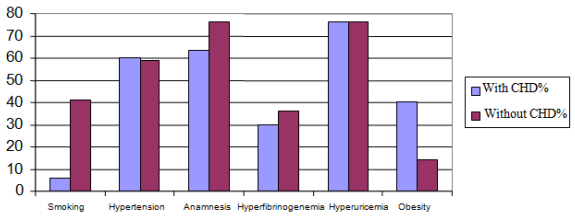

Figure 5: Non-lipid risk factors in diabetes patients with and without CHD

The possible existence of the improper distribution of non-lipids risk factors according to gender was investigated by Fisher's exact probability test. The significantly higher occurrence of obesity in women has been demonstrated at the level of $p = 0.05$.

The existence of differences in the frequency of non-lipids risk factors in patients with CHD and diabetes patients without CHD was determined by Fisher's exact probability test.

Table 1: Non-Lipid Risk Factors in Patients with and without CHD

	Without CHD	With CHD	P
WHR	0.92 ± 0.04	0.90 ± 0.04	NS
TA systolic (mmHg)	156.72 ± 3.17	147.7 ± 22.7	NS
TA diastolic (mmHg)	96.81 ± 10.86	90.34 ± 14.2	< 0.05
Glycemia (mmol/l)	7.37 ± 2.19	8.9 ± 2.67	< 0.05
MBG (mmol/l)	9.34 ± 2.28	11.61 ± 2.7	< 0.01
Fibrinogen (g/l)	3.66 ± 1.3	3.68 ± 1.4	NS
Acidum urici (mmmol)	292.08 ± 87.14	294 ± 102.74	NS
Diabetic experience (year)	6.4 ± 7.35	7.6 ± 5.84	NS

The percentage of smokers was much higher among the patients without CHD compared to diabetics with CHD (41% vs. 6%, $p < 0.01$). Obesity was relatively rare, however, with patients who did not have CHD compared to diabetes patients with CHD group (13.6% vs. 40%, $p < 0.01$).

The possible role of anthropometric and biochemical indicators of CHD with dyslipidemic diabetes patients was analysed statistically. Obesity expressed as the mean BMI was significantly higher in patients with CHD 29.67 + 3.31 about diabetes patients without coronary disease 3.17 ± 27.8 kg/m^2. Abnormal glucose regulation was perceived as the

fasting plasma glucose and daily mean glycemic profile. These disorders were more prevalent with patients with CHD; FBG 8.9 ± 2.67 vs. 7.37 ± 2.19 mmol/1 ($p < 0.05$) and MBG 11.61 ± 2.7 vs. 9.34 ± 2.82 mmol/l ($p < 0.01$). In contrast to more favourable profile values of all parameters in patients without CHD, diastolic blood pressure values were significantly higher in diabetes patients without CHD 96.81 ± 10.86 vs. 90.34 ± 14.2 mmHg than in patients with coronary artery disease.

Discussion

It is known, according to the data from the expert literature that over 60% of homeless diabetics (IDPs) had manifested dyslipidemia [8]. In this original work, elevated lipid levels of risk (high-risk + border) cholesterol (HOL) was investigated for this type of patients.

These health problems had 90% of the patients (with CHD and 76% without CHD), which proved to be statistically significant ($\chi 2 = 6.12$, $p < 0.05$). A higher percentage of patients in the group with CHD had elevated lipid levels and risk for triglycerides (TG) 70% compared to patients without CHD, 56.5% ($\chi 2 = 4.36$, $p < 0.05$). Other parameters did not show significant differences in the distribution between the two groups.

Coronary disease in a non-diabetic population is far more prevalent in men younger than 65, compared to women of the same age. However, in diabetes patients, this difference do not exist; furthermore, women with diabetes are far more vulnerable to early morbidity and mortality from CHD [10]. This was confirmed in this study, where women with diabetes were slightly younger (57.5 ± 23.7 vs. 58.8 ± 9.3) and with longer disease duration (9.2 ± 6.71. vs. 6.12 ± 7.13, $p < 0.05$) compared to men.

In the group of diabetes patients with dyslipidemia and coronary disease, some of the parameters of syndrome X were discovered in abundance. Hyperuricemia was found in 76% of patients, obesity in 40% and hypertension in 60% of cases. A positive family history was present in 63.3%, which supports the claims of the existence of the hereditary genetic defect in syndrome X.

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Mother-Father Differences in Postnatal Psychological Distress and Its Determinants in Iran

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Abstract

AIM: The aim of this study was to investigate the mother-father differences in Postnatal Psychological Distress (PPD) and its determinants among the parents with 8-weeks old children.

MATERIALS AND METHODS: In this cross-sectional study, applying simple random sampling, 306 postnatal parents with an 8-weeks old infant in Saqqez County, Iran, were invited to answer the General Health Questionnaire-28 (GHQ-28) items through the telephone interview. Fifty-eight subjects declined to participate in the study (Response Rate = 81.04%). The data were analysed using the SPSS Statistics v. 21.

RESULTS: About 16.9% of all the parents had PPD. The difference in the prevalence of PPD in three dimensions between the two groups were statistically significant ($p < 0.01$): social dysfunction (25.8% for fathers vs. 5.6% for mothers), somatic disorders (21% for fathers vs. 7.3% for mothers), and anxiety (21% for fathers vs. 6.5% for mothers). The mode of delivery of the mothers and the level of education, the number of children, monthly income, and being consent with pregnancy among the fathers were significant predictors for PPD.

CONCLUSION: The level of PPD was more prevalent among the new fathers compared to the new mothers. Among the fathers, but not the mothers, socioeconomic characteristics were contributed to PPD. Considering the differences in risk factors for maternal and paternal PPD, our findings may help family health care providers and policymakers in designing gender-specific intervention programs and diagnosis tools aimed at PPD prevention among new parents.

Introduction

Based on the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), maternal PPD is the onset of a major depressive episode occurring within the first month of delivery [1]. The depressive episodes may include marked loss of interest in virtually all activities, fatigue or loss of energy, depressed or sad mood, diminished ability to think or concentrate, psychomotor agitation or retardation, significant weight loss or gain, feelings of worthlessness or guilt, insomnia or hypersomnia, and recurrent thoughts of death. The diagnosis of a mother with a major depressive episode requires presenting five of these symptoms for two weeks, and at least one of the symptoms is either depressed mood or sadness or a remarkable decreased pleasure or interest in all or almost all activities [1].

Kim and Swain [2] in a review study categorized the risk factors of PPD in three domains including biological risk factors (such as low level of testosterone, estrogen, cortisol and prolactin), ecological risk factors (such as change in lifestyle, difficulties in developing attachment with infant and changing in marital relationship) and lack of prevention and intervention programs to support the parents in transition to parenthood during the

postpartum period. Therefore, the post-partum period can be a high-risk time for the onset of severe mental illness among mothers [3]. Post-partum depression is one of the most common complications of childbirth among new mothers [4], with the prevalence rate of 12 to 35% [5-8]. On the other hand, among new fathers, postnatal negative somatic and psychological symptoms have also been reported in previous studies [9, 10].

Paternal postnatal depression among new fathers may be considered as a familial health issue. Edoka et al., in a study on the healthcare costs of postnatal depression, found the paternal post-partum depression to be associated with increased community care costs such as primary care, psychologist contacts, and more outpatient hospital services utilisation [11]. Paternal postnatal depression has negative impacts on family health including the care of children [12]. It may, also, increase the level of stress and tension in the family and result in behavioural and emotional disorders including hyperactivity, depression, anxiety and delayed language development among children [13, 14]. Previous studies have shown that fathers with a good level of psychological well-being can have a protective effect against the maternal depression and its side effects on the child [15, 16]. Moreover, children with two depressed parents are at an elevated risk for social, psychological and cognitive deficits [17, 18].

Previous studies have shown that the postnatal depression among new fathers is prevalent [19]. The rate of diagnosed anxiety or depressive disorders during postnatal period among new fathers has been estimated to be around 2–5% [20, 21]. Goodman reported a variant incidence rate (1.2% to 25.5%) for paternal postnatal depression among different communities [10]. Recently, public awareness about the psychological well-being of the new fathers during the postnatal period has been increased. However, this issue has not well been examined, to date [12]. Despite the reports in the literature on the associations between paternal psychological well-being and the increasing rate of post-partum depression among new mothers [10, 12, 22], the studies investigating the mother-father differences in Postnatal Psychological Distress (PPD) and its determinants are few.

The aim of this study was to investigate the mother-father differences in PPD and its determinants among the parents with 8-weeks old children in Saqqez County, Iran. The following questions guided the study: (1) what is the prevalence of PPD among the new parents? (2) What are the father-mother differences in the domains of PPD among the new parents? (3) Are the determinants of PPD and its domains are different between the new mothers and fathers?

Material and Methods

Study Design and Participants

A cross-sectional study was conducted on 248 postnatal parents with an 8-weeks old infant in Saqqez County, Iran, from July to September 2015. The couples were recruited from the maternity ward of the Saqqez Imam Khomeini Hospital.

The sample size was determined considering the proportion of postpartum depression among the new mothers (20%-40%) [23] and fathers (1.2- 25.5%) [10]. Given a 95% of confidence level and the power of 80%, in two-tailed tests using G-Power 3.1.2 software, the sample size was calculated to be, at least, 306 subjects. From the total number of 306 parents selected through simple random sampling, 58 subjects declined to participate in the study (Response Rate = 81.04%). Thus, 248 parents (124 mothers and 124 fathers) included in the study and constituted the sample for the data analyses.

Those parents with a healthy 8-weeks old infant, no severe cognitive impairment (according to the participant's health records in the maternity centres) and living in urban areas (to have home phone number) were included in the study. Additional eligibility criteria included being able to be interviewed through telephone (with no hearing impairment), being consent to participate in the study, and not too busy to join the telephone interview.

The phone number of the home of respondents was retrieved from the records in the maternity ward-where the delivery took place. Eight weeks after the birth of their child, the parents were called by the head of maternity ward and invited to participate in the study and all signed a consent form. After the invitation, all the parents were called by telephone at two different times (morning for mothers and evening for fathers), and during the telephone contacts, they were interviewed about 28 items of the General Health Questionnaire-28 (GHQ-28). Therefore, all data including socio-demographic and psychological wellbeing status were gathered by telephone interview. This study was approved by the Ethical Committee of Tabriz University of Medical Sciences.

Measures

A two-section questionnaire was used to collect data. The first section was related to the demographic characteristics of the respondents including age, occupation (employed/unemployed), level of education (illiterate, elementary, high school, diploma, university), number of children (1, 2, 3, more than 3), level of monthly income (low, moderate, high), type of delivery (Cesarean Section/ Natural Vaginal Delivery) and being consent with pregnancy (Yes/No).

The second part was the Iranian version of General Health Questionnaire (GHQ-28) [24] used to assess the psychological well-being among the parents. This instrument, as one of the most widely used questionnaires to measure psychological distress in medical settings, was developed as a screening tool to detect psychiatric disorders and emotional distress among different populations. As several previous studies have applied the different versions of GHQ-28 in studies related to perinatal psychological distress [25-27], we also chose to use it for measuring postnatal psychological distress among the parents in the present study. The GHQ-28 encompasses four mental health dimensions: somatic symptoms, anxiety, social dysfunction, and depression [28]. Each dimension consists of 7 items. In the current study, the questionnaire was scored according to the Likert-type scaling (0, 1, 2, and 3) and the cut-off point = 23 was considered during data analysis. Based on this scoring, the total score ranges from 0 to 84, in which the higher score indicates, the more symptoms of psychological distress. In a previous study, the Persian version of GHQ-28 with the cut-off score of 23 showed sensitivity, specificity and overall misclassification rate of 70.5%, 92.3% and 12.3%, respectively [29]. The participants with the GHQ-28 score less than 23 were classified as the group with low psychological distress and the participants with the GHQ-28 score more than 23 were classified as the group with high psychological distress.

Data analysis

The data were expressed as number and percentage for qualitative variables. The differences between the two sets of data were evaluated using Chi-square test. After splitting the data by gender, simple linear regression analysis was conducted to examine the demographic characteristics as independent variables and the psychological distress and its domains as dependent variables. The data were analysed using the statistical software package IBM SPSS Statistics v. 21. P-values less than 0.05 were considered as statistically significant.

Results

Table 1 shows the distribution of PPD among the respondents based on the demographic variables. In total, 26 (21%) fathers and 16 (12.9%) mothers had GHQ > 23, but there was no statistically significant difference between the two groups. More than two-thirds of the participants were less than 39 years old (89.5%). The most of the parents with psychological distress were older than 39 years (GHQ>23). Forty-eight percent of the parents had a primary level of education, who, mostly, had PPD (p = 0.038). More than two-thirds (87.5%) of the parents had a maximum of two children. Significant differences were found in PPD of the parents by their level of education (p = 0.036) and their number of children (p = 0.036).

Table 1: Psychological distress among the parents by their demographic characteristics

Variable	Low Psychological Distress*	High Psychological Distress**	Total	P-value
	No. (%)	No. (%)	No. (%)	
Parent				
Father	98 (79%)	26 (21%)	124 (50%)	0.127
Mother	108 (87.1%)	16 (12.9%)	124 (50%)	
Age				
18-28	88 (83%)	18 (17%)	106 (42.7%)	0.649
29-39	98 (84.5%)	18 (15.5%)	116 (46.8%)	
Older than 39	20 (76.9%)	6 (23.1%)	26 (10.5%)	
Job				
Employed	98 (47.6%)	25 (59.5%)	123 (49.6%)	0.178
Unemployed	108 (52.4%)	17 (40.5%)	125 (50.4%)	
Education level				
Illiterate	18 (8.7%)	5 (11.9%)	23 (9.3%)	0.038*
Elementary	94 (45.6%)	25 (59.5%)	119 (48%)	
High school	26 (12.6%)	8 (19 %)	34 (13.7%)	
Diploma	48 (32.3%)	4 (9.5%)	52 (21%)	
University	20 (9.7%)	---	20 (8.1%)	
Number of Children				
1	93 (45.1%)	17 (40.5%)	110 (44.4%)	0.036*
2	91 (44.2%)	16 (38.1%)	107 (43.1%)	
3	19 (9.2%)	5 (11.9%)	24 (9.7%)	
More than 3	3 (1.5%)	4 (9.5%)	7 (2.8%)	
Monthly Income				
Low	63 (30.6%)	17 (40.5%)	80 (32.3%)	0.277
Moderate	143 (69.4%)	25 (59.5%)	168 (67.7%)	
High	-	-	-	
Delivery type				
CS†	96 (46.6%)	14 (33.3%)	110 (44.4%)	0.128
NVD¥	110 (53.4%)	28 (66.8%)	138 (56.6%)	
Being Consent with Pregnancy				
Yes	175 (85%)	35 (83.3%)	210 (84.7%)	0.817
NO	31 (15%)	7 (16.7%)	38 (15.3%)	

* GHQ<23;** GHQ>23; †CS: Cesarean Section; ¥NVD: Normal Vaginal Delivery.

Table 2 shows the father-mother differences in PPD and its four dimensions between the two groups of parents. About 16.9% of all the parents had PPD. The difference in the prevalence of PPD in three dimensions between the two groups were, statistically, significant (p< 0.01): social dysfunction (25.8% for fathers vs. 5.6% for mothers), somatic disorders (21% for fathers vs. 7.3% for mothers), and anxiety (21% for fathers vs. 6.5% for mothers).

Table 2: Father-mother differences in psychological distress and its dimensions among the parents

Variables	Fathers	Mothers	Total	P-value
	No. (%)	No. (%)	No. (%)	
Somatic Disorder				0.003
Yes	26 (21%)	9 (7.3%)	35 (14.1%)	
No	98 (79%)	115 (92.7%)	213 (85.9%)	
Anxiety				
Yes	26 (21%)	8 (6.5%)	34 (13.7%)	0.001
No	98 (79%)	116 (93.5%)	214 (86.3%)	
Social dysfunction				
Yes	32 (25.8%)	8 (6.5%)	40 (16.1%)	0.000
No	92 (74.2%)	116 (93.5%)	208 (83.9%)	
Depression				
Yes	14 (11.3%)	16 (12.9%)	30 (12.1%)	0.846
No	110 (88.7%)	108 (87.1%)	218 (87.9%)	
Psychological distress				
Yes	26 (21%)	16 (12.9%)	42 (16.9%)	0.127
No	98 (79%)	108 (87.1%)	206 (83.1%)	

Table 3 shows demographic variables as predictors for PPD and its dimensions among the parents. Adjusted linear regression showed that the mode of delivery among the new mothers predicted

8% of somatic disorders, 5% of anxiety/insomnia, 2% of severe depression and 12% of the total PPD. On the other hand, the level education, the number children and monthly income predicted 37% of anxiety/insomnia among the new fathers. Moreover, the level of education and monthly income predicted 6% of social dysfunction. Again, among the fathers, the level of education and being consent with pregnancy predicted 7% of severe depression, and, also, the level of education and the number of children predicted 18% of total PPD.

Table 3: Differences in predictors of psychological distress and its dimensions among the parents

Dependent variables	Parents	Independent variables	B	p-value	95% CI	Adjusted R^2
Somatic symptoms	Fathers		----	----	-----	----
	Mothers	Mode of Delivery	-1.27	0.002	-2.05 to -0.49	0.08
Anxiety/insomnia	Fathers	Education level	-0.96	0.001	-1.26 to -0.66	0.37
		Children number	0.79	0.01	0.18 to 1.4	
		Income status	-1.11	0.003	-1.83 to -0.39	
	Mothers	Mode of Delivery	-1.09	0.01	-1.92 to -0.27	0.05
Social dysfunction	Fathers	Education level	0.40	0.047	0.53 to 0.80	0.06
		Income status	0.97	0.049	0.41 to 1.93	
	Mothers		----	----	-----	----
Severe depression	Fathers	Education level	-0.20	0.046	-3.99 to -0.003	0.07
		Being Consent with Pregnancy	-0.80	0.015	-0.16 to -1.44	
	Mothers	Mode of Delivery	-0.91	0.004	-1.53 to -0.300	0.02
Psychological distress	Fathers	Education level	-0.787	0.001	-1.22 to -0.34	0.18
		Number of children	1.46	0.002	0.55 to 2.36	
	Mothers	Mode of Delivery	-3.69	0.001	--5.31 to -2.07	0.12

Discussion

The purpose of this study was to investigate the father-mother differences in PPD and its determinants among Iranian parents with 8-weeks old children. Somatic disorders, anxiety and social dysfunction, were more prevalent among the new fathers, compared to the new mothers. Among the mothers, the mode of delivery was contributed to psychological distress and all its dimensions, except for social dysfunction. In contrast, among the fathers, the level of education was associated with PPD and all its dimensions, except for somatic symptoms. Moreover, among the fathers, but not mothers, the number of children and monthly income predicted some domains of psychological distress. Being consent with pregnancy was, also, contributed to severe depression among the new fathers.

The findings of the present study showed that PPD (GHQ-28 score ≥ 23) was more prevalent among the new fathers (21%), compared to the new mothers, which was higher than those reported (2.1% to 12.4%) in the previous studies [14, 21, 30, 31]. In contrast, a frequency of 12.9% was found for PPD among the new mothers who were similar to those reported in previous studies (3.2% to 27.5%) [27, 32]. These different frequencies found in literature may be due to the different times of conducting the studies after delivery, the different instruments (or different cut-off points) utilised, and different cultural and ethnic groups explored in the different studies. In Japan, the prevalence of PPD among mothers four months after delivery was 7.7% [27]. In Italy, 6 to 8 weeks after delivery, the prevalence was 13% [26], and in England, this amount, 3–6 months after that delivery, was 23.46% [32]. Also, postpartum depression among the new fathers in a US community-based sample was 4 to 25% [33] and in a population-based longitudinal study in Bristol was 1.2 to 11.9% [14]. In agreement with those reported in a previous study [34], the new fathers may be faced with PPD as a result of their unpreparedness for the speed changes taking place in their family life and, also, their unawareness from the range and depth of the demands they will face. Another reason may be due to difficulties in playing the paternal role, as a new role is being added to the other routine roles a father may have in his daily life. For instance, fathers in Iran have the least contact with the health system during the pregnancy period of their wives, when the mothers are provided with prenatal health care. This may prepare the mothers, but not the fathers, for gradually adopting the parental role. Consequently, after childbirth, fathers are come across with an unknown new role resulting in a level of psychological distress.

In the present study, social dysfunction, somatic disorders and anxiety were more prevalent among the new fathers in comparison with the new mothers. In other words, eight weeks after delivery, fathers were more nervous, worried, helpless, anxious, and less energetic and self-confident in proportion to the mothers. These findings are in line with those reported by Matthey et al. [20]. Similarly, Morse et al., in a study on first-time parenthood found that the predictors of distress among the new fathers was low emotional support from partner, high negative affect, low dyadic adjustment, as well as high gender role stress, resulted from fears of performance failure [31].

The findings of the present study along with those reported, previously, showed remarkable differences in PPD between the new fathers and the new mothers. This difference manifests the different needs of fathers from those of mothers which urge the need for different studies with, probably, different methodologies to detect and measure the differences [35]. Separate studies with different approaches will help in designing different interventional programs with different strategies for them. For example, qualitative studies on how different the new fathers experience postnatal parenthood from the new mothers and why such differences may exist may be helpful in providing a more diverse findings for better evidence-based practice.

In the present study, having a lower level of education and having three children and more were

associated with PPD among the new fathers. Similarly, Deater-Deckard et al., also, found that lower level of educational qualifications and older age were associated with higher levels of depressive symptoms among the fathers after child birth [36]. Similar associations have been reported in several previous studies [6, 25, 37]. As it can be expected, with an increase in the number of children for a less-educated father, he may be confronted with more complex issues which may be difficult to manage due to a low level of education. Such situations may result in a higher risk for PPD.

The findings showed that the mode of cesarian section (CS) delivery among the mothers was associated with the higher rates of somatic symptoms, anxiety/insomnia, and severe depression, as well. This result is in line with those reported by Borders, who noted that mothers with CS after seven weeks had significantly worse levels of physical functioning, mental health, pain, social functioning, and daily activities [38, 39]. The mothers with CS experience more depression and PPD by 3.58 times compared to the mothers with Normal Vaginal Delivery (NVD) [34]. As a result, women with CS may have more long-term morbidity compared to the mothers with NVD [38, 40].

In the present study, the level of education, the number of children and monthly income predicted about 37% of anxiety/insomnia among the fathers. Moreover, among the fathers, but not the mothers, the level of education and monthly income, as well as the level of education and being consent with pregnancy, were significantly associated with social dysfunction and severe depression, respectively. In consistent with these findings, up to one-third of the new fathers may experience depressive symptoms or have PPD after their baby's birth [41, 42]. The lack of job opportunities in marginal areas like Saqqez County, forces fathers to migrate to other prosperous cities to look for work which results in worries about disruptions in the family structure [43]. Moreover, in such underprivileged marginal communities with the low level of employment, giving birth to a child may cause anxiety to the new fathers who may, in turn, results in somatic disorders, insomnia and social dysfunction, as well.

The number of studies investigating the mother-father differences in PPD and its determinants is scarce. However, there were limitations to the present study. Data collection was via phone call, and it was not possible for the researchers to invite the parents for face to face interview. Moreover, as the PPD of the new parents may be associated with the health status of their new infant [44], the authors had to investigate the health status of their new born infant.

The findings of the present study may be considered as evidence for differences in PPD and its determinants between the new parents. It was concluded that the level of PPD is more prevalent among the new fathers compared to the new mothers. Among the new fathers, but not the new mothers, socioeconomic characteristics were contributed to PPD. Family health care providers, midwives and family physicians should better understand the differences in PPD among the new parents. Considering the differences in risk factors for maternal and paternal PPD, our findings may help family health care providers and policymakers in designing gender-specific intervention programs and diagnosis tools aimed at PPD prevention among new parents. A routine screening program for PPD among the new fathers is, also, recommended.

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Review Article

Retained Surgical Foreign Bodies after Surgery

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Abstract

The problem of retained surgical bodies (RSB) after surgery is an issue for surgeons, hospitals and the entire medical team. They have potentially harmful consequences for the patient as they can be life threatening and usually, a further operation is necessary. The incidence of RSB is between 0.3 to 1.0 per 1,000 abdominal operations, and they occur due to a lack of organisation and communication between surgical staff during the process. Typically, the RSB are surgical sponges and instruments located in the abdomen, retroperitoneum and pelvis.

Introduction

Retained surgical bodies (RSB) are any foreign bodies left inside the patient after the operation and in general, a further procedure is necessary. The consequence of foreign bodies after surgery may manifest in different forms immediately after the operation, months or even years after the surgical procedure. With more than 28 million operations performed nationwide, the number of cases in which foreign bodies are left behind during a procedure in the United States has been estimated at around 1500 cases per year [1, 2]. Surgery is challenging, with the risk of retained surgical bodies increasing particularly in complicated cases such as obese patients or trauma requiring the use of numerous instruments, retractors and surgical sponges. During surgery, systems are in place to create a safe environment for the patient while the surgeon works with sponges and instruments; however, they are not impervious to human error.

Commonly, the discovery of the foreign bodies after surgery occurs due to non-specific complaints. The retained bodies can present as a mass usually in the abdominal cavity and are diagnosed during a routine radiological examination. If patients complain in the period after the operation of pain, frequent infections and a palpable mass, this would suggest the presence of retained surgical bodies.

Regarding the type of RSB, sponges are the most many foreign bodies retained in the human body after surgery, being located in body cavities such as the abdomen, pelvis and retroperitoneal space. These sponges may remain in the body for days, months or even years before manifesting as inflammatory reactions. When retained bodies are suspected, diagnosis must be confirmed by computed tomography (CT) [3]. In addition, surgical instruments such as clamps, retractors, electrodes or drains can be left behind after operations, especially in the abdominal cavity [4]. Instruments made of stainless steel, like retractors, may evoke minimal reactions but

all foreign bodies have the potential to cause pain, obstruction, ileus or abscess. According to the literature, approximately 80% of cases diagnosed with RSB are those in which the number of declared materials was correct at the end of the operation [5, 6]. Good communication inside the operating room is essential for minimal errors during surgery. The retention of RSF after surgery has medical and legal implications, occurring as a result of mistakes by the entire medical team, not just the surgeon.

Before every operation instruments are counted by the scrub nurse and as a standard procedure, they are counted at the end of the procedures to ensure that they have all been accounted for, and nothing has been left behind in the patient. Counting instruments during operations is difficult, especially during emergency surgery such as abdominal trauma, in which the whole team is engaged in treating the patient.

Clinical manifestation of retained surgical bodies after surgical procedure

The RSB can manifest differently depending on their location and the type of material. They can remain in the nose, inside of the tracheobronchial tree, retroperitoneal space, uterus, and spine; however, they are commonly located in the abdominal cavity. RSB inside the abdominal cavity can produce pain, abdominal tumours that can raise suspicions for malignant mass, intraabdominal abscess, obstructive ileus, intestinal perforation, gastrointestinal fistula, bleeding and can migrate transmurally[7].

They can clinically manifest as acute reactions like an inflammatory response, infection or abscess within days or weeks after the operation. Furthermore, retained surgical foreign bodies inside the body cavity may also manifest as aseptic inflammation or exudative without infection, leading to nonspecific manifestation [8]. Patients may complain of pain and discomfort months or years after their procedure, especially in those cases where sponges remain [9]. Acute reactions after surgical procedures require immediate attention for further diagnosis and urgent surgery to remove the foreign body.

The further operation to retrieve the RSB is very successful if performed soon after the first procedure, typically within two weeks. At this stage, they can be detected by X-ray or can manifest as an inflammatory reaction. In such cases, a reasonable approach is first to attempt to remove the RSB laparoscopically. In the case of chronic manifestation months or even years after the first procedure, it is important to perform a CT scan first as a tumour-like mass or bowel obstruction, as well as various types of fistulae may be involved [7, 10]. Often, malignant tumours are suspected in such chronic manifestations, so CT and MRI scans are important to establish a diagnosis.

The RSB can be organised as a mass inside the abdominal cavity, and a tumour may be suspected [11], in which case, extensive diagnostic imaging can distinguish the RSB from a tumour mass. Fibrinous changes present as a soft tissue mass in about 27% [12] or as an aseptic RSB that can result in granulomatous reactions and adhesions. In some cases, RSB may be organised in an abscess and manifest with clinical signs of sepsis [13].

RSB may also manifest as inflammation in the area surrounding the retained surgical sponge and may be associated with a bowel obstruction [14]. These cases require immediate surgery once it has been established that the RSB is causing the blockage. The RSB can lead to perforation of the intestinal wall and pathological communication between the adjacent structures [7]. This erosion can result in fistula formation, another form of complication related to retained foreign bodies [15, 16]. Gastrointestinal bleeding from the upper gastrointestinal tract can also occur and may be life threatening for the patient, requiring urgent treatment with clinical restitution [17]. Transmural migration of the RSB after surgery can cause an intestinal obstruction when the RSB migrates from the abdominal to intraluminal space of the bowel [18]. Surgery is required to resolve this complication.

As previously mentioned, the most commonly retained surgical items are sponges due to their extensive use, especially when surgeons are dealing with trauma and massive bleeding [19]. Surgical sponges are referred to as "gossypiboma" or "textiloma" [1].

How to prevent RSB during surgical procedures

Approximately 88% of RSB cases occur in a situation where the sponge and instrument counts were declared “correct” [1]. Counting the surgical materials used during the surgical procedure is the responsibility of the nurses under a direction of the doctors. The Association of Operating Room Nurses published an uptodate.com policy in 2015 recommending the points below that are widely used in the United States hospitals [20]. Specifically, counts should be performed at the following time points during the procedure: - before the procedure begins (initial count); - whenever new additional items are used during the operation; - before the surgeon closes

the body cavity; - when the surgeon begins to close the wound; and - when the surgeon closes the skin (final count).

This accounting system was developed as part of the United States National Surgical Patient Safety Project (nothing left behind) with the aim to prevent retained surgical items [21].

Methods

Literature Review

The literature was searched via Pub Med, Scientific Commons and Google Scholar databases using the search term 'foreign bodies after surgery'. Only articles in the English language were included in the review.

Results

In total, more than 30 articles were found related to retained surgical bodies after surgery, reporting different reasons for the preserved bodies being left inside the operation field after the surgical procedure. According to Gawande and Al, in the majority of cases where sponges were left behind, the number of sponges before closing was always declared correct, suggesting that counting alone is not sufficient. In addition, studies showed that body mass index, intraoperative complications and unexpected events are associated with an increased risk for retained bodies after surgical procedures [22]. Furthermore, authors, in their study of 34 cases with retained surgical bodies, concluded that a breakdown in communication within the operation team was the most important factor in relation to the issue of surgical bodies [23].

Finally, the studies reviewed recommended that the best strategies to prevent retained surgical bodies were good communication in the operation theatre, systematic counting of materials used during the surgical procedure, use of tracking devices for electronic sponge counts and counting before the cavity and skin are closed.

Discussion

The aim of this review was to identify weakness in the surgical team's performance which may result in foreign bodies being left in body cavities. The retention of foreign bodies is an issue for all surgical procedures but is often associated with cases of traumatic injury at the emergency unit and during elective operations requiring different teams during the surgical procedure. The diagnosis of an RSFB is based upon imaging studies, and if an RSFB is suspected in the immediate postoperative period, plain radiographs of the surgical field should be performed.

Radiopaque surgical instruments and devices should be immediately apparent on plain film and the characteristic appearance of radiopaque tape or wires of laparotomy pads and surgical sponges, respectively, should indicate their presence. The diagnosis of retained bodies can also be made using CT and gastrointestinal contrast studies.

Excellent communication within the surgical team was identified as a major factor to minimise the number of surgical bodies left after surgical operations in the body cavity. Therefore, to eliminate the occurrence of RSFB, the surgical team must work together to ensure a safe operation and good post-operative outcomes; excellent communication during the procedure between the surgeons, nurses and anaesthetists is key to success.

In conclusion, RSFB are still common despite new surgical techniques and equipment. The key to preventing the incidence of RSB is excellent communication within the surgical team, between the surgeons, nurses and anaesthetists.

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