Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Sep 12; 10(B):2098-2103.
https://doi.org/10.3889/oamjms.2022.10461
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Endocrinology*

The Impact of Early Levothyroxine Replacement in Subclinical Hypothyroidism on Glycemic Control Parameters and Quality of Life in Adult Patients

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Mowafy M, Rushdy EA, Rakha M, Elshekheiby E, Soliman S. The Impact of Early Levothyroxine Replacement in Subclinical Hypothyroidism on Glycemic Control Parameters and Quality of Life in Adult Patients. Open-Access Maced J Med Sci. 2022 Sep 12; 10(B):2098-2103. https://doi.org/10.3889/oamjms.2022.10461
Keywords: Subclinical hypothyroidism; Substitution; Quality of life; Glycemic control
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Received: 18-Jun-2022
Revised: 30-Aug-2022
Accepted: 02-Sep-2022

Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists

Abstract

BACKGROUND: Subclinical hypothyroidism is diagnosed by increased level of serum thyroid-stimulating hormone (TSH) with normal levels of free triiodothyronine (FT3) and free thyroxine (FT4). Controversy exists concerning the early treatment of subclinical hypothyroidism with levothyroxine when TSH level is below 10 mIU/L.

AIM: This stud aims to quantify the effects of a 3-month trial of levothyroxine replacement on quality of life in SCH patients with TSH level less than 10 mIU/L as primary outcome and fasting blood sugar and HbA1C levels as secondary outcome.

METHODS: This was a randomized controlled trial. It was carried out on subjects between 18 and 65 years, of both sexes attending the family medicine outpatient clinic at Cairo University Hospitals with untreated symptomatic mild subclinical hypothyroidism. Simple randomization was performed by assigning random numbers from random number table. Quality of life (Short-Form 36 Questionnaire) as well as fasting blood sugar levels and HbA1C were assessed before the replacement of levothyroxine and 3 months after starting treatment in the subclinical hypothyroidism patients (intervention group) and were compared to the control group.

RESULTS: The median of role limitations due to emotional problems, social functioning, and health change was higher in the intervention group in comparison with the control group. Moreover, the median scores of all general health questionnaire items showed significant positive statistical changes in the intervention group. There was also a significant improvement in glycemic control reflected in lower HbA1C levels and FBS.

CONCLUSION: The results of our study highlight the positive effect of early substitution with levothyroxine in subclinical hypothyroid patients regarding the quality of life and glycemic control in Egypt and support the argument for replacement.

Introduction

Subclinical hypothyroidism is defined as elevated serum thyroid-stimulating hormone (TSH) with normal levels of free triiodothyronine (FT3) and free thyroxine (FT4). It is a biochemical finding based on the TSH concentration higher than 4.12 mIU/L or over the age-adjusted upper normal level as it was proposed by the American and European Thyroid Associations (ATA/ETA) and the American Association of Clinical Endocrinologists [1], [2].

The prevalence of SCH is 4–10% in general population worldwide, showing higher frequency in women. In people over the age of 60, the prevalence of SCH significantly increases and reaches 15% in females and 8% in males [3].

The reference intervals for TSH depends on age, sex, ethnicity, body mass index (BMI), and pregnancy status may need to be determined before SCH can be clearly diagnosed. TSH distribution curves also seemed to shift upward with increasing age [4]. The most widely recognized cause for SCH and overt hypothyroidism is Hashimoto thyroiditis [5].

Controversy exists concerning the early treatment of subclinical hypothyroidism with levothyroxine when TSH level is below 10 mIU/L. In fact, patients below 70 years with a TSH level <10 mIU/L, the diagnosis of SCH is not always followed by levothyroxine (LT4) replacement. Since 2008, most guidelines agreed that most individuals with TSH under 10 mIU/l do not need treatment [6]. On the other hand, the ETA guideline stated that the choice for replacement depends on the presence of mild symptoms suggesting hypothyroidism, goiter, or other comorbidities [2].

Pandrc *et al.* (2017) advised LT4 replacement only if elevation in TSH persists for more than 3 months in patients with multiple risk factors for the development of overt hypothyroidism with re-evaluation of the effects

of treatment after 3 months. Those who do not fulfill these criteria are followed up for 6 months [7].

SCH has been shown to have detrimental effects on health. Various aspects of patient quality of life as emotional and mental well-being have been negatively affected in this subset of patients. Furthermore, SCH was also found to be associated with insulin resistance in type 2 diabetic patients and worsening of glycemic (HbA1C) (Skarulis *et al.*, 2010). Despite this, studies supporting early levothyroxine replacement in SCH have shown conflicting results [8].

The aim of our study was to assess the impact of a 3-month trial of LT4 treatment on the quality of life and glycemic status in SCH patients with TSH <10 mIU/L providing possible evidence supporting early introduction of levothyroxine replacement in this subset.

Subjects and Methods

Study setting

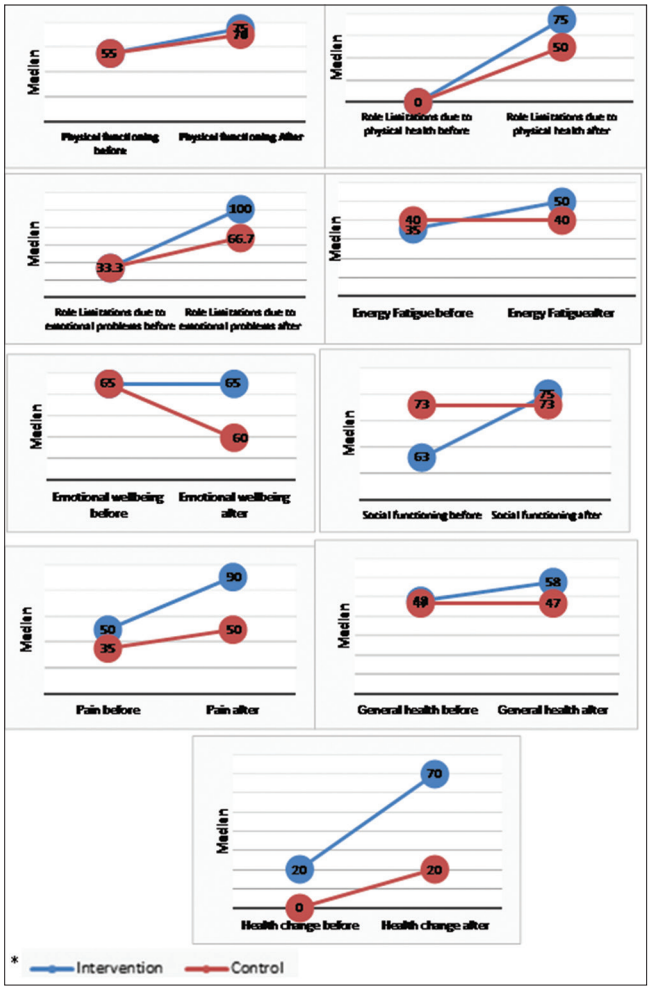
This study was carried out on patients with untreated subclinical hypothyroid attending outpatient the family medicine clinics at Kasr Al-Ainy Hospital, Cairo University, from June 2019 to September 2020.

Study design

This study was a randomized controlled clinical trial carried out on patients with untreated subclinical hypothyroidism. Simple randomization for the interventional group and the control group was performed by assigning random numbers from random number table. The aim was to assess the impact of early levothyroxine replacement for subclinical hypothyroidism on health-related quality of life in the interventional group as a primary outcome and effect on glycemic control as a secondary outcome before and after commencement of levothyroxine replacement in comparison to the control group.

Medical history and examination were done to confirm inclusion and exclusion criteria. General examination including anthropometric measurements; blood pressure, weight, and height for calculating BMI (BMI = kg/m^2 where kg is a person's weight in kilograms and m^2 is their height in meters squared). A BMI of 25.0 or more is overweight, while the healthy range is 18.5–24.9 and BMI equal or more than 30 is obese [9].

Inclusion criteria of patients were all persons (aged 18–65 years old) attending the family medicine outpatient clinics at Kasr Al-Ainy Hospital with untreated subclinical hypothyroidism defined as TSH level between 4.5 mIU/L and 10 mIU/L with normal FT4. Exclusion criteria of patients were subjects currently



Figures 1: Changes in quality of life parameters before and after therapy in the intervention and control groups

prescribed levothyroxine, antithyroid drugs, amiodarone or lithium, recent thyroid surgery or radioiodine (within the previous 12 months), previous history of thyroid disease or treatment, and conditions that affect thyroid status and pregnancy.

Table 1: Baseline demographic characteristics of patients in the intervention and control groups

Sex	Intervention, n (%)	Control, n (%)	p-value
Male	5 (11.1)	7 (15.6)	0.535
Female	40 (88.9)	38 (84.4)	
Governorate			
Cairo	20 (44.4)	21 (46.7)	0.423
Giza	18 (40)	13 (28.9)	
Others	7 (15.6)	11 (24.4)	
Region			
Urban	13 (28.9)	11 (24.4)	0.634
Rural	32 (71.1)	34 (75.6)	
Marital status			
Single	9 (20)	9 (20)	1
Married	31 (68.9)	32 (71.1)	
Divorced	2 (4.4)	1 (2.2)	
Widow	3 (6.7)	3 (6.7)	
Educational level			
Not educated	9 (20)	14 (31.1)	0.14
Basic education	13 (28.9)	5 (11.1)	
Secondary education	8 (17.8)	12 (26.7)	
University and above	15 (33.3)	14 (31.1)	
History			
Thyroid disease	0 (0)	0 (0)	0.343
DM	10 (22.7)	10 (21.7)	
Hypertension	3 (6.8)	5 (10.9)	
None of above	30 (68.2)	26 (56.5)	
DM and hypertension	1 (2.3)	5 (10.9)	

Sample size calculation was done using the comparison of general health (GH) subscale of SF36 questionnaire before and after treating cases with subclinical hypothyroid state [10].

Ninety patients underwent random allocation and were assigned to two groups A and B: Group A included 45 subjects with untreated SCH that was started on levothyroxine for 3 months as intervention group. Group B included 45 subjects with untreated SCH as a control group.

Oral consent was taken from all the participants. Levothyroxine (ranging from 25 mcg to 75 mcg for 6–8 weeks) was started for the intervention group after full explanation of its effectiveness and side effects. Patients of both groups: Intervention and control were followed up for 3 months. Thirty-six short-form questionnaires (translated and validated Arabic version) [11] were administered at the first visit and 3 months later to both the control group and the intervention group (after replacement of levothyroxine).

The Short-form 36 Health Survey questionnaire is intended to assess the different aspects of health status and well-being, both physical and mental [12]. It consists of 36 items, arranged into eight domains: GH, physical function, social function, mental health, vitality, emotional, physical, and bodily pain. Every domain ranges from 0 to 100 points, in which 100 points give the maximum score and the highest satisfaction with quality of life, while 0 point gives the lowest score and the least satisfaction with quality of life [9], [13]. Accompanied with the SF-36 questionnaire, participants were asked to give demographic information for their age, sex, and level of education.

Statistical analysis

IBM computer using Statistical Program for the Social Sciences version 21 was used for analysis of data as follows: Description of quantitative variables as median and IQR according to Shapiro test of normality and description of qualitative variables as percentage and number. Chi-square test was used to compare qualitative variables between groups. Fisher's exact test was used when one expected cell or more is <5. Unpaired t-test was used to compare quantitative variables in parametric data (SD <30% mean). Mann–Whitney U-test was used instead of unpaired t-test in non-parametric data (SD >30% mean). $p > 0.05$ was considered statistically insignificant. $p < 0.05$ was considered statistically significant [14].

Results

A total number of patients included in this clinical trial were 90 patients (intervention group = 45 patients and control group = 45 patients). Regarding the demographic characteristics, there was no significant difference between two groups (Table 1).

Regarding the anthropometric data and clinical characteristics, there was no significant statistical difference between the intervention and control groups in the first visit before intervention except in the systolic blood pressure. There was a significant difference between the intervention and control groups ($p = 0.002$) but all the readings were within the normal range of blood pressure readings (Table 2).

Table 2: Baseline anthropometric, clinical, glycemic, and hormonal data in the intervention and control groups at the first visit (MV±SD)

Baseline-anthropometric,clinical, glycemic and hormonal data	Intervention	Control	p-value
	Median (IQR)	Median (IQR)	
Weight 1st visit	78 (62:85)	78 (62:93)	0.449
Body mass index 1st visit	31.3 (26.4:34.4)	31 (26.2:37.6)	0.949
Systolic blood pressure 1st visit	111 (108:121)	120 (110:130)	0.002
Diastolic blood pressure 1st visit	71 (63:78)	73 (68:75)	0.507
Hemoglobin A1C 1st visit	5.3 (5.1:5.6)	5.4 (4.9:6.5)	0.096
Fasting blood sugar 1st visit	92 (85:106)	97 (87:115)	0.276
Thyroid-stimulating hormone 1st visit	7.2 (5.9:8.5)	6.4 (5.8:7.4)	0.039
Free Triiodothyronine level (free T3) 1st visit	2.9 (2.4:3.5)	3.3 (2.3:4.2)	0.277
Free thyroxine level (free T4) 1st visit	12.1 (11:13.6)	12.3 (11.1:13.3)	0.774

In the second visit, there was still a significant statistical change in the systolic blood pressure between the intervention and control groups ($p = 0.002$). Regarding the HbA1C, FBS, and TSH, there was a significant reduction in the intervention group ($p = 0.003$, 0.05, and 0.02, respectively) Table 3.

Table 3: Comparison of anthropometric, clinical, glycemic, and hormonal data after 3 months in the intervention and control groups (MV±SD)

Anthropometric, clinical, glycemic and hormonal data	Intervention	Control	p-value
	Median (IQR)	Median (IQR)	
Systolic blood pressure 2nd visit	115 (109:120)	120 (117:130)	0.002
Diastolic blood pressure 2nd visit	74 (67:78)	75 (70:80)	0.131
Weight 2nd visit	77 (62:84)	78 (63:93)	0.268
Body mass index 2nd visit	30.8 (26.2:33.4)	31.7 (26.8:37.6)	0.177
Hemoglobin A1C 2nd visit	5.1 (4.7:5.5)	5.5 (4.9:6.2)	0.003
Fasting blood sugar 2nd visit	93 (84:103)	102 (85:122)	0.05
Thyroid-stimulating hormone 2nd visit	5 (3.6:6.4)	5.8 (4.7:7.3)	0.02
Free triiodothyronine level (Free T3) 2nd visit	3.3 (2.5:3.9)	3.5 (2.5:4.4)	0.299
Free thyroxine level (Free T4) 2nd visit	13.2 (11.8:14.2)	13.3 (12.1:14.8)	0.508

In the intervention group, the median of free T4 was statistically significantly higher after intervention in pre- versus in post-intervention ($p = 0.002$). There was evident reduction in weight, BMI, HbA1C, and TSH ($p = 0.03$, 0.006, <0.001, and <0.001, respectively) (Table 4).

Table 4: Comparison of anthropometric, clinical, glycemic, and hormonal data before and 3 months after replacement in the intervention group

Anthropometric, clinical, glycemic and hormonal data	Intervention		p-value
	Pre	Post	
	Median (IQR)	Median (IQR)	
Weight	78 (62:85)	77 (62:84)	0.03
Body mass index	31.3 (26.4:34.4)	30.8 (26.2:33.4)	0.006
Systolic blood pressure	111 (108:121)	115 (109:120)	0.726
Diastolic blood pressure	71 (63:78)	74 (67:78)	0.688
Hemoglobin A1C	5.3 (5.1:5.6)	5.1 (4.7:5.5)	<0.001
Fasting blood sugar	92 (85:106)	93 (84:103)	0.241
Thyroid-stimulating hormone	7.2 (5.9:8.5)	5 (3.6:6.4)	<0.001
Free triiodothyronine level (Free T3)	2.9 (2.4:3.5)	3.3 (2.5:3.9)	0.053
Free thyroxine level (Free T4)	12.1 (11:13.6)	13.2 (11.8:14.2)	0.002

Regarding the GH questionnaire items, there was no significant statistical difference between the intervention and control groups in the first visit except in the health change, there was a significant difference (p = 0.05) (Table 5).

Table 5: Comparison of general health questionnaire items at the first visit between the intervention and control groups

General health questionnaire items	Intervention	Control	p-value
	Median (IQR)	Median (IQR)	
Physical functioning before	55 (35:65)	55 (35:85)	0.125
Role limitations due to physical health before	0 (0:50)	0 (0:75)	0.929
Role limitations due to emotional problems before	33.3 (0:100)	33.3 (0:66.7)	0.604
Energy fatigue before	35 (30:50)	40 (35:50)	0.094
Emotional well-being before	65 (50:70)	65 (50:75)	0.661
Social functioning before	62.5 (25:75)	72.5 (37.5:87.5)	0.448
Pain before	50 (20:85)	35 (20:75)	0.932
General health before	48 (33:64)	47 (33:67)	0.783
Health change before	20 (0:70)	0 (0:20)	0.05

Regarding the GH questionnaire items after intervention between the intervention and control groups, there was no significant statistical differences between them in physical functioning, role limitations due to physical health, energy fatigue, emotional well-being, pain, and GH. On the other hand, the median of role limitations due to emotional problems, social functioning, and health change was higher in intervention group (100) (66.7:100), 75 (72.5:87.5), 70 (70:100) versus 66.7 (33.3:100), 72.5 (35:75), and 20 (0:70) in the control group, respectively (p = 0.014, 0.002, and 0.018) (Table 6).

Table 6: Comparison of general health questionnaire items after 3 months between the intervention and control groups

General health questionnaire items	Intervention	Control	p-value
	Median (IQR)	Median (IQR)	
Physical functioning after	75 (60:85)	70 (45:90)	0.99
Role limitations due to physical health after	75 (50:100)	50 (0:100)	0.076
Role limitations due to emotional problems after	100 (66.7:100)	66.7 (33.3:100)	0.014
Energy fatigue after	50 (35:60)	40 (30:60)	0.181
Emotional well-being after	65 (55:80)	60 (50:75)	0.296
Social functioning after	75 (72.5:87.5)	72.5 (35:75)	0.002
Pain after	90 (50:100)	50 (35:100)	0.179
General health after	58 (38:74)	47 (28:73)	0.372
Health change after	70 (70:100)	20 (0:70)	0.018

The median of all GH questionnaire items showed positive significant statistical changes after intervention (Table 7).

Table 7: Comparison of general health questionnaire items before and 3 months after replacement in the intervention group

Intervention			
General health questionnaire items	Pre	Post	p-value
	Median (IQR)	Median (IQR)	
Physical functioning	55 (35:65)	75 (60:85)	<0.001
Role limitations due to physical health	0 (0:50)	75 (50:100)	<0.001
Role limitations due to emotional problems	33.3 (0:100)	100 (66.7:100)	<0.001
Energy fatigue	35 (30:50)	50 (35:60)	0.002
Emotional well-being	65 (50:70)	65 (55:80)	0.048
Social functioning	62.5 (25:75)	75 (72.5:87.5)	<0.001
Pain	50 (20:85)	90 (50:100)	<0.001
General health	48 (33:64)	58 (38:74)	<0.001
Health change	20 (0:70)	70 (70:100)	<0.001

Regarding the GH questionnaire items comparison between the control group in the first and second visit, there was no significant statistical differences between them in energy, fatigue, emotional well-being, social functioning, and GH. On the other hand, there were statistically significant differences regarding the remaining items (Table 8).

Table 8: Comparison of general health questionnaire items before and 3 months later in the control group

General health questionnaire items	Control		p-value
	Pre	Post	
	Median (IQR)	Median (IQR)	
Physical functioning	55 (35:85)	70 (45:90)	0.002
Role limitations due to physical health	0 (0:75)	50 (0:100)	0.002
Role limitations due to emotional problems	33.3 (0:66.7)	66.7 (33.3:100)	<0.001
Energy fatigue	40 (35:50)	40 (30:60)	0.915
Emotional well-being	65 (50:75)	60 (50:75)	0.858
Social functioning	72.5 (37.5:87.5)	72.5 (35:75)	0.876
Pain	35 (20:75)	50 (35:100)	0.035
General health	47 (33:67)	47 (28:73)	0.809
Health change	0 (0:20)	20 (0:70)	0.001

Figure 1 demonstrates the significant improvement in various quality of life parameters in the intervention group after 3 months of levothyroxine replacement in comparison to the control group.

Discussion

Numerous studies have uncovered that even mild subclinical hypothyroidism may pose an additional risk factor for decreased quality of life, cardiovascular, and metabolic diseases. In our study, we aimed to evaluate the beneficial effect of early levothyroxine replacement on patient's quality of life parameters and glycemic control.

Up to date, the evidence supporting early levothyroxine substitution as regards improvement of the quality of life specifically is limited. Although SCH has been shown to negatively affect the quality of life [15], studies of levothyroxine therapy in subclinical hypothyroidism have shown conflicting outcomes [16]. One large randomized controlled trial investigated the effects of substitution with levothyroxine on SCH in participants older than 65 years of age and it showed no added benefit to substitution with levothyroxine as regards the quality of life [17].

In the present study, replacement with levothyroxine was initiated in patients with TSH levels <10 mIU/l and with normal free T3 and free T4 levels. Our outcomes showed that minimal correctional doses of levothyroxine (ranging from 25 mcg to 75 mcg for 6–8 weeks) were accompanied with statistically significant improvement in numerous items of the GH questionnaire such as physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy fatigue, emotional well-being, social functioning, pain, GH, and health change 3 months after levothyroxine replacement in the interventional group. Moreover, there was an overall elevation of SF-36 questionnaire scores after levothyroxine supplementation.

Similar results were revealed in a study by Reuters *et al*. [10] that L-T4 may improve some physical aspects of quality of life measured by the SF-36 questionnaire, despite the absence of statistically

significant improvement in clinical score. LT4 treatment for 6 months showed mild improvement of psychological aspects in subclinical hypothyroidism.

Our study results are supported by the data of a study by Milena which addressed the impact of early introduction of levothyroxine in SCH on quality of life in Serbia[7]. It is worth noting that this study supported replacement with higher than average doses in this subset of patients. It proposed treatment with a higher starting dose of levothyroxine (50–100 mg) or target values TSH <2.5 mmol/L except for very old individuals.

Insulin resistance, hyperglycemia, elevated blood pressure, and obesity are all incremented in the development and progression of cardiometabolic disease. SCH was found to be associated with increased insulin resistance in type 2 diabetic patients and worsening of glycemic (HbA1C) control [8]. Our results demonstrated a statistically significant reduction in HbA1C after levothyroxine treatment in the intervention group.

It was emphasized by Edina *et al*., 2012, that there is a significant effect of replacement with levothyroxine on glycemic control in patients with subclinical hypothyroidism [18]. The correlation between TSH and HbA1c was positive and significant after 6 months of treatment.

The improvement of quality of life items appears to be a relevant indicator in monitoring the therapeutic effect of early correction of subclinical hypothyroidism and in addition provides strong supporting evidence to early replacement by levothyroxine. The positive effect on glycemic control after levothyroxine further strengthens the argument for its early introduction.

The limitations of the study include the relatively short duration of the trial; hence, the long-term effects of levothyroxine replacement could not be addressed. In addition, the non-availability of patients due to the shutdown of family medicine clinics secondary to the start of the COVID-19 pandemic affected the sample size which could have otherwise been increased.

Conclusion

Available data from our study highlight the positive effect of early substitution with levothyroxine in subclinical hypothyroid patients regarding the quality of life and glycemic control and support the argument for early replacement. The improvement of GH quality of life could be relevant indices in evaluation and follow-up of the effect of early substitution.

Recommendations

Based on the results of this research, we recommend more long-term multicentric studies with larger sample size to assess the effect of early replacement of levothyroxine in subclinical hypothyroid on the quality of life. More investigations are needed to determine the optimal dosages of levothyroxine in different subset of patients with SCH.

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