Achieving euthyroidism in hypothyroid patients using levothyroxine improves depressivity and impaired daily life scores using ThyPRO questionnaire

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Background
Levothyroxine is the recommended treatment to achieve euthyroidism in hypothyroid patients. Achieving euthyroidism was found to improve quality of life in some studies but failed to do so in other studies. Thyroid patient reported outcomes (ThyPRO) is a thyroid-specific health-related quality of life measure. This study aims to assess patient-reported outcomes in levothyroxine-treated hypothyroid patients using ThyPRO.

Patients and methods
The study included 194 patients, divided into two groups: group 1 included 141 hypothyroid patients with benign thyroid disease treated with l-thyroxine, stable in euthyroidism for at least 6 months, and group 2 included 53 patients with euthyroid benign thyroid disease. All patients completed a professionally translated, carefully revised version of the ThyPRO questionnaire into Arabic language. All patients had their Thyroid stimulating hormone (TSH) measured at inclusion. Anti-thyroperoxidase and/or anti-thyroglobulin antibodies were recorded for each patient where available.

Results
There were no significant differences between the two studied groups regarding age, sex, and TSH. Anti-thyroperoxidase antibodies were significantly higher in treatment group versus group 2, but anti-thyroglobulin antibodies did not differ among the two studied groups. Group 1, l-thyroxine treatment group, showed significantly lower scores in the goiter symptoms, depressivity, impaired daily life, and hyperthyroid symptom scales compared with group 2. No significant differences were found regarding the remaining symptom scales.

Conclusion
Hypothyroid patients of different etiologies rendered euthyroid for at least 6 months compared with euthyroid patients with benign thyroid disease have significantly better depression, goiter, impaired daily life scores using a thyroid-specific questionnaire, the ThyPRO, compared with euthyroid benign thyroid disease.

Keywords:
depressivity, goiter symptoms, hypothyroidism, impaired daily life, levothyroxine

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Introduction

Hypothyroidism is the second most commonly prevalent endocrine disorder after diabetes mellitus. Prevalence of hypothyroidism is 4.6 and 4.9% in USA and Europe, respectively [1,2]. Accordingly, l-thyroxine is the first of the top 10 medicines in the USA in the past 4 years in terms of prescriptions dispensed [3]. Research studies have shown that levothyroxine treatment for hypothyroidism, even subclinical hypothyroidism, improved many health-related quality of life (QoL) aspects including depressive symptoms, attention performance, and physical and mental aspects of health-related QoL [4–9]. However, other studies have shown no benefit of thyroxine treatment in hypothyroid patients regarding hypothyroid symptom scores and health-related QoL [10–14]. Nonspecific tools were used to evaluate these patients like SF-36 questionnaire, symptom checklist-90-revised, Beck depression inventory, hospital anxiety and depression scale, general health questionnaire, sickness impact profile, Billewicz and Zulewski scores, Hamilton rating scale for depression, and Hamilton scale for anxiety. Thyroid patient reported outcomes (ThyPRO) is a thyroid-specific comprehensive questionnaire that measures the effect of benign thyroid disease on health-related QoL. A recent meta-analysis recommended the assessment of health-related QoL in patients with benign thyroid diseases using ThyPRO [15,16].

The aim of this study is to evaluate patient-reported outcomes as a measure of treatment satisfaction in hypothyroid patients with different etiologies treated with levothyroxine versus patients with euthyroid benign thyroid diseases not receiving levothyroxine using a thyroid-specific health-related QoL measure, the ThyPRO.

Patients and methods

The study was conducted on 194 patients with benign thyroid disease. They were divided into two groups: group 1 included 141 patients with hypothyroidism owing to benign thyroid diseases treated with l-thyroxine, and group 2 included 53 patients with euthyroid benign thyroid disease. Group 1 patients were rendered euthyroid by treatment. They were stable in euthyroidism for at least 6 months before inclusion in the study.

Exclusion criteria included hypothyroidism, hyperthyroidism, thyroid carcinoma, past history or current treatment for psychiatric illness (depression or anxiety disorders), diabetes, and chronic liver or kidney diseases.

Alexandria Faculty of Medicine ethical committee approved the protocol of the study, and all study participants provided a written informed consent after being explained the nature and aim of the study.

Methods

All patients completed a professionally translated, carefully revised version of the ThyPRO questionnaire into Arabic language. ThyPRO consists of 84 questions, grouped in 13 scales, namely, goiter symptoms, hyperthyroid symptoms, eye symptoms, hypothyroid symptoms, tiredness, cognition, anxiety, depressivity, emotional susceptibility, impaired social life, impaired daily life, impaired sex life, cosmetic complaints, and one single question that measures general health-related QoL. Sex life domain was deliberately omitted from the questionnaire, because asking about sex life is not accepted culturally by most Egyptian patients. Each question was scored on a five-point scoring system from 0=not at all to 4=very much, with a 4-week reference period. The multiquestion scales were derived by averaging question scores within a scale and linearly transforming them to a 0–100 scale with 0 being the best and 100 being the worst possible score [17].

All patients had their Thyroid stimulating hormone (TSH) measured at inclusion to ensure euthyroidism. Anti-thyroperoxidase antibodies and/or anti-thyroglobulin antibodies were recorded for each patient where available.

Data were analyzed using IBM SPSS software package version 20.0 (IBM Corp., Armonk, New York, USA). Significance of the obtained results was judged at the 5% level.

Results

Group 1 included 141 patients with benign thyroid disease treated with l-thyroxine. Their diagnoses were 102 Hashimoto thyroiditis, 22 total thyroidectomies, seven de Quervain's thyroiditis, five postpartum thyroiditis, and five other diagnoses. All of them were stable in euthyroidism 6 months before inclusion in the study. Group 2 included 53 patients with euthyroid benign thyroid disease, and their diagnoses were 22 patients with euthyroid Hashimoto thyroiditis, 22 patients with nodular thyroid disease (uninodular or multinodular disease), six patients with graves' disease in remission, and three patients with other diagnosis (lobectomy and resolved de Quervain's thyroiditis).

Both study groups were matched for age. Mean age was 37.6 years for group 1 and 38.6 years for group 2 (P=0.642). Most patients of both groups were female: 92.2% of group 1 and 90.6% of group 2 (P=0.771). Mean TSH for both groups was similar: 1.5 mIU/l for group 1 and 1.9 mIU/l for group 2 (P=0.051; Table 1).

Because 72.3% of group 1 were patients with Hashimoto thyroiditis versus only 41.5% of group 2, anti-thyroperoxidase antibodies were significantly higher in treatment group versus group 2 (P=0.026), but anti-thyroglobulin antibodies did not differ between the two studied groups (P=0.637; Table 1).

Regarding the ThyPRO questionnaire, group 1, l-thyroxine treatment group, showed significantly lower scores in the goiter symptoms, depressivity, impaired daily life, and hyperthyroid symptom scales compared with group 2. No significant differences were found regarding the other eight symptom scales and the question assessing general health-related QoL between the two studied groups (Table 2 and Fig. 1).

Discussion

The main results of this study are that hypothyroid patients after 6 months of achieving euthyroidism using l-thyroxine showed better scores on

Table 1 Comparison between the two studied groups according to age, sex, TSH at inclusion, and thyroid autoantibodies

	Total (n=194)	Treatment		Test of significance	P
		Treated (n=141)	Untreated (n=53)		
Age (years)					
Median (minimum–maximum)	37 (14–70)	37 (14–70)	36 (17–68)	t=0.466	0.642
Mean±SD	37.9±12.8	37.6±12.4	38.6±14.1		
Sex					
Male	16 (8.2)	11 (7.8)	5 (9.4)	χ^2=0.136	0.771
Female	178 (91.8)	130 (92.2)	48 (90.6)		
TSH					
Median (minimum–maximum)	1.5 (0.2–3.8)	1.5 (0.2–3.8)	1.7 (0.3–3.8)	U=3055.5	0.051
Mean±SD	1.6±0.8	1.5±0.7	1.9±1		
Anti-TG					
Median (minimum–maximum)	171.5 (12–4000)	154 (17.6–4000)	187 (12–1370)	U=902.0	0.637
Mean±SD	367.2±645.2	397.8±720.6	280.3±348.1		
Anti-TPO					
Median (minimum–maximum)	149.5 (1–1300)	203 (1–1135)	72 (5–1300)	U=1134.5	0.026*
Mean±SD	258.6±281.7	288.3±280.7	174.9±271.5		

t, P: t and P values for Student t-test for comparing between the two groups. U, P: U and P values for Mann–Whitney test for comparing between the two groups. TSH, thyroid stimulating hormone; χ^2, P: χ^2 and P values for χ^2-test for comparing between the two groups. Anti-TG, anti-thyroglobulin; Anti-TPO, anti-thyroperoxidase. *$P \leq 0.05$, statistically significant.

depressivity, impaired daily life, goiter, and hyperthyroid symptom scales using ThyPRO compared with patients with benign thyroid disease who are euthyroid without treatment.

Control group in this study included patients with euthyroid benign thyroid disease not receiving thyroxine therapy rather than healthy controls for two reasons, first: to adjust for the psychological burden of having a chronic illness, and second: to adjust for the effects of medical care, even without treatment, on health status perception, which is expected to increase self-awareness of health status, in other words, to exclude a placebo-like effect of medical care [4,8,18].

Hypothyroidism, both overt and subclinical, have been associated with impaired physical, mental, and general aspects of QoL [13,18,19]. Untreated overt and subclinical hypothyroidism was associated with two-fold higher prevalence of depression compared with normal control [20,21]. Fatigue and impaired exercise tolerance are proven consequences of subclinical hypothyroidism [13,22]. Anxiety and disability scores assessed by Hamilton anxiety rating scale and brief disability questionnaire are higher in overt hypothyroidism compared with healthy controls [19].

Many trials aimed to evaluate the effect of l-thyroxine treatment on symptomatic burden and QoL in hypothyroid patients with variable results originating from variable study designs. Duration of l-thyroxine treatment ranged from only 3 to 6 months like this study and up to 1 year or more in others. Numbers of hypothyroid patients included in most of the studies were less than 50–100 patients, and only a minority included more than a hundred hypothyroid patients like this study. Most of them included only patients with subclinical hypothyroidism, but only a few included patients with both overt and subclinical hypothyroidism like this study. Some studies were prospective, blinded, and placebo controlled, whereas others were cross-sectional cohorts like this study. Finally, few studies included one-fifth to one-third of their patient not achieving euthyroidism at the time of evaluation [4–14,19,20,22–27].

Depressive symptoms are the main psychiatric symptoms in hypothyroid patients affecting 60%. A serotonin – TRH feedback loop may explain the association between depression and hypothyroidism [19,28]. Against the results of this study, six studies reported worse depression scores in hypothyroid patients despite achieving euthyroidism using l-thyroxine, for a duration ranging from 3 months to more than a year, compared with normal control [6,10–12,24,27]. On the contrary, five studies showed an improvement of depression scores in hypothyroid patients achieving euthyroidism using l-thyroxine, for a duration ranging from 3 to 9 months, compared with normal control [6,7,19,20,26].

Of special interest, Quinque *et al.* [27] showed that using a thyroid-specific patient-reported outcome measure called thyroid symptom rating questionnaire, hypothyroid patients achieving euthyroidism using l-thyroxine for a mean duration

Table 2 Comparison between the two studied groups according to mean % score of different domains of the ThyPRO questionnaire

Mean % score	Total (*n*=194)	Treatment		*U*	*P*
		Treated (*n*=141)	Untreated (*n*=53)		
Goiter symptoms					
Median (minimum–maximum)	7.5 (0–100)	6.8 (0–50)	11.4 (0–100)	2851.0*	0.011*
Mean±SD	12.2±14	10.4±11.3	17±18.8		
Hyperthyroid symptoms					
Median (minimum–maximum)	18.8 (0–95.8)	18.8 (0–75)	21.9 (0–95.8)	3034.5*	0.044*
Mean±SD	22.8±17.8	20.8±15.7	28.1±21.7		
Eye symptoms					
Median (minimum–maximum)	12.5 (0–81.3)	12.5 (0–81.3)	15.6 (0–75)	3502.5	0.500
Mean±SD	16.9±16.6	16.5±16.7	17.7±16.5		
Hypothyroid symptoms					
Median (minimum–maximum)	12.5 (0–75)	12.5 (0–75)	18.8 (0–75)	3432.0	0.377
Mean±SD	21.2±20.4	19.9±19	24.5±23.5		
Tiredness					
Median (minimum–maximum)	39.3 (0–100)	39.3 (0–100)	42.9 (7.1–100)	3202.0	0.124
Mean±SD	40.6±19.4	38.9±18.3	45.1±21.6		
Cognition					
Median (minimum–maximum)	25 (0–100)	25 (0–100)	20.8 (0–100)	3616.5	0.730
Mean±SD	27.4±24.2	27.1±24.2	28.1±24.4		
Anxiety					
Median (minimum–maximum)	37.5 (0–100)	33.3 (0–100)	45.8 (0–100)	3244.5	0.157
Mean±SD	42±26.2	40.4±25.9	46.3±26.7		
Depressivity					
Median (minimum–maximum)	39.3 (0–100)	35.7 (0–89.3)	46.4 (14.3–100)	2950.5*	0.024*
Mean±SD	42.1±21	40±20.8	47.8±20.8		
Emotional susceptibility					
Median (minimum–maximum)	41.7 (0–94.4)	38.9 (4.2–94.4)	44.4 (0–80.6)	3118.0	0.076
Mean±SD	41.3±18.1	40±17.6	44.9±19.4		
Impaired social life					
Median (minimum–maximum)	18.8 (0–100)	18.8 (0–100)	18.8 (0–93.8)	3572.5	0.784
Mean±SD	24.2±23.8	23.6±23.1	25.8±25.8		
Impaired daily life					
Median (minimum–maximum)	4.2 (0–100)	4.2 (0–75)	8.3 (0–100)	2897.5*	0.021*
Mean±SD	15.8±21.3	13.9±19.6	21±24.7		
Cosmetic concern					
Median (minimum–maximum)	4.2 (0–100)	8.3 (0–100)	4.2 (0–100)	3464.5	0.594
Mean±SD	16±22.9	16.5±23.3	14.4±22		
Has your thyroid disease had a negative effect on your quality of life?					
Median (minimum–maximum)	0 (0–100)	0 (0–100)	0 (0–100)	3541.5	0.814
Mean±SD	18.8±25.4	18.9±25.9	18.8±24.2		

U, *P*: *U* and *P* values for Mann–Whitney test for comparing between the two groups. *$P \leq 0.05$, statistically significant.

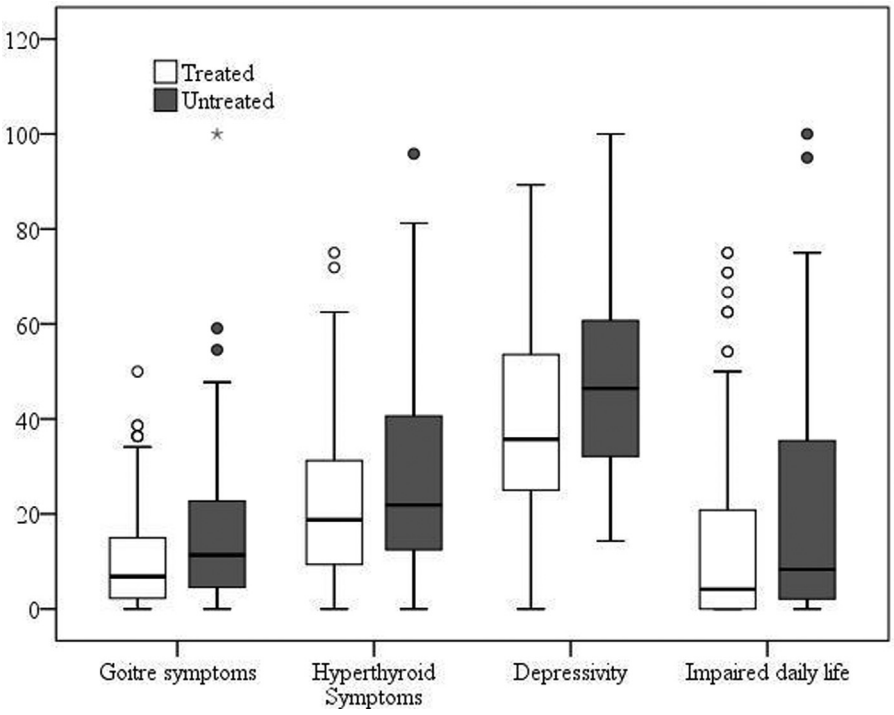
of 7.5 years had worse depressive scores compared with normal controls. However, Winther *et al.* [26] using the same tool used in this study – ThyPRO – after achieving euthyroidism for the same duration – 6 months – reported that depressivity scores improved and became similar to general population.

Several possible explanations have been proposed to explain the persistence of depression in hypothyroid patients despite achieving euthyroidism for a long time.

Thyroid autoimmunity, even with euthyroidism, has been associated with Hamilton and Edinburgh depression scale scores in two separate studies, indeed 76% of the l-thyroxine treatment group and 53% of the control group experienced autoimmune thyroid disease [28].

Obesity, commonly associating hypothyroidism and not improved by achieving euthyroidism per se, may be another explanation. Kelderman-Bolk *et al.* [10] found that obesity correlates with poor QoL in hypothyroid patients after achieving euthyroidism. On reviewing the literature, they found that obesity impairs same QoL subscales as those impaired in their cohort of hypothyroid on L-T4 therapy for 6 months.

Figure 1



Comparison between the two studied groups according to mean % score of depressivity, impaired daily life, goiter, and hyperthyroid symptoms.

TSH cutoff limit to define euthyroidism in relation to depression may be a third factor. Talaei *et al.* [24] suggested that a TSH level of more than 2.5 mIU/l can predict depressive symptoms with 93.7% accuracy, and a TSH level of less than 2.5 mIU/l can rule out depressive symptoms, with 81% accuracy. Mean TSH for both groups in this study were 1.5 and 1.9 mIU/l, respectively, which means that most treated patients achieved a TSH level of less than 2.5 mIU/l. This study findings support the cutoff limit suggested by Talaei *et al.* [24] given the better depressivity scores in treated patients.

Tissue hypothyroidism is a lack of availability of T3 at tissue levels - in this case the brain tissues - owing to either a deiodinase or a thyroid hormone transporter defect, thus limiting either availability or cellular transport of T3, respectively. *DIO2* (T3 generation in the brain) and *OATP1C1* (thyroid hormone transport to the brain) gene polymorphism may contribute to persistent depressive symptoms despite adequate L-T4 therapy [28].

Psychological burden of chronic illness and chronic treatment may induce a psychopathological disease. Having at least one chronic physical illness increases the likelihood of having depression up to 23% compared with a likelihood of only 3.2% in absence of a chronic illness. Awareness of a disease state may alter mood and behavior in people susceptible for depression. For this reason, we have chosen the control group to be patients with euthyroid benign thyroid disease to control for the burden of chronic illness and placebo effect of medical care other than L-T4 therapy [18,29].

The second important finding in this study is a better score on impaired daily life scale. Unlike this study findings, euthyroidism for variable durations was associated with nonimprovement in tiredness, fatigue, exercise tolerance, and physical domains of QoL [10,11,22,25–27]. However, other studies reported an improvement in fatigue, frequency of tiredness, and physical/somatic aspects of QoL [5,6,8,13,23]. Some of the studies that report worse tiredness used a thyroid-specific patient-reported outcome questionnaire; however, all other studies reported improvement used a generic QoL measurement tool. Thyroid-specific tools are better capable of detecting treatment effect compared with generic ones. Thus, this study is the first to report improvement in daily life using a thyroid-specific tool, the ThyPRO [15].

This study also showed a better score in the goiter symptom scale among the treatment group. Unlike this study, Winther *et al.* [26] using ThyPRO, the same

tool in this study, showed a persistently higher goiter symptom score despite adequate L-T4 treatment for 6 months, which is also the same duration of euthyroidism in this study. Only three differences between this study and the study by Winther *et al.* [26] could explain different results: only 78 hypothyroid patients in their study versus 141 in this study; they included only patients with autoimmune hypothyroidism, whereas the present cohort included 24% with nonautoimmune hypothyroidism; and finally, they compared their cohort to general population, whereas in the present cohort, the control group included patients with euthyroid benign thyroid disease [26].Finally, this study also showed a lower score in the hyperthyroid symptom scale among the treatment group. Hyperthyroid symptoms mimic those of anxiety. Literature showed worse anxiety scores on hospital depression and anxiety scale after treatment with l-thyroxine for 6 months in two separate studies, a treatment duration that is similar to this study [10,13]. Better depressivity scores may as well suggest lower psychological burden, which may explain the significantly lower hyperthyroid symptom score in treated patients in this study.

The major limitation of this study is the lack of patient-reported outcomes for the treatment group before the initiation of L-T4 therapy; this may have allowed a longitudinal comparison of patient-reported outcomes before and after l-thyroxine treatment.

Strengths of this study include the large number of hypothyroid patients evaluated compared with many other cited studies including less than a hundred patients, an adequate duration of euthyroidism of 6 months compared with only 3 months in many of the cited articles, the use of patients with euthyroid benign thyroid disease as a control group to control for the burden of having a chronic illness on the results, and finally, the use of a thyroid-specific questionnaire, the ThyPRO, which is validated to measure the effect of treatment on thyroid disease burden in benign thyroid disease.

Conclusion

Hypothyroid patients of different etiologies rendered euthyroid for 6 months compared with euthyroid patients with benign thyroid disease have significantly better depression, goiter, impaired daily life, and hyperthyroid symptoms scores using a thyroid-specific questionnaire, the ThyPRO, compared with euthyroid benign thyroid disease.

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Conflicts of interest

There are no conflicts of interest.

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