Does Being Biochemically Euthyroid Guarantee Complete Well-Being among Primary Hypothyroid Patients in Zagazig University Hospital?

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Abstract

Background: Hypothyroidism is one of the commonest hormonal deficiencies, which is associated with high somatic and psychiatric morbidity. **Objective**: This study was done to assess quality of life (QoL), satisfaction with life and treatment among hypothyroid patients and to correlate level of control, disease duration and free Triiodothyronine (T3)/Thyroxine (T4) ratio to these outcome measures. **Method:** A cross-sectional study was applied on 257 hypothyroid patients in Zagazig University hospital from September 2019 to March 2020. All patients filled in thyroid quality of life, satisfaction with life, thyroid symptom, and satisfaction with thyroid treatment questionnaires. Thyroid profile was assessed**. Results:** Females represented 66.9% with mean age 44.175 years. Regarding Thyroid-stimulating hormone (TSH), patients were divided into; uncontrolled, controlled and strictly controlled, which represented 26.5%, 35.8% and 37.7% respectively. Reduced FT3/FT4 prevailed in 40.5%. There were non-significant relation between level of control and QoL; present, hypothyroid dependent, importance rating or total thyrDol 18 scores. There was statistically significant relation between level of control and each of thyroid treatment satisfaction, satisfaction with life score and thyroid symptom scores. There was statistically significant relation between T3/T4 ratio and each of present, total thyrDol 18, thyroid treatment satisfaction, satisfaction with life score and thyroid symptom scores. Athyreotic patients had better QoL and SWLS. **Conclusion:** Achieving biochemical well-being not essentially means physical wellbeing. TSH alone can render patients biochemically euthyroid yet the patients still suffer. Reduced T3/T4 ratio impaired QoL which pointed to importance of development of management strategy rather than relying only on TSH levels.

Keywords: *Quality, wellbeing, satisfaction*

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Introduction

Clinical primary hypothyroidism is mainly a laboratory-based diagnosis, which is characterized by presence a serum TSH level more than the reference range (0.4–4.5 mIU/L) and low free T4.[1] Hence, diagnosis of primary hypothyroidism exclusively bases on measurement of pituitary TSH.[2] There is strong evidence that somatic and psychiatric morbidities prevail among those patients, which eventually impaired health related quality of life.[3-6]

Owing to non-specific chronic-like nature of hypothyroid symptoms, it has a noteworthy negative influence on self-reported health status.[7] Levothyroxine

replacement therapy is the main stay for treatment of hypothyroidism. Therapeutic goals set comprise resolution of symptoms, signs, normalization of serum TSH, and evading overtreatment (iatrogenic thyrotoxicosis), especially in the elderly.[2]

To achieve euthyroid state (by TSH normalization), Free T4 values must be significantly higher than in euthyroid controls. Despite that, serum FT3 is significantly lower than in normal subjects. The patients had an extremely heterogeneous T3 production capacity, suggesting that peripheral T4 to T3 conversion may not be appropriate enough to preserve a normal FT3/FT4 ratio using levothyroxine monotherapy. All of that throws patients, into living a sustained state of abnormal thyroid hormone availability for the peripheral tissues, despite normalization of TSH.[8]

Method

This study was done to assess quality of life, satisfaction with life and treatment among patients with hypothyroidism on treatment and to correlate level of control, disease duration and T3/T4 ratio to these outcome measures.

A cross-sectional study was recruited on hypothyroid patients attending Endocrine outpatient clinic, Internal Medicine department, Zagazig University hospital from September 2019 to March 2020. All patients attended the clinic during study period and fulfilled inclusion criteria were enrolled.

Case definition: Presence a serum TSH level more than the reference range (0.4–4.5 mIU/L) and low free T4 (reference range; 0.8 to 1.8 nanograms per deciliter (ng/dL)

Inclusion criteria: Patients with established primary hypothyroidism on treatment with levothyroxine morning dose aged from 18 to 60 years. Normal and overweight pre-obese BMI (from 18 to 29.99 kg/m^2). No other associated comorbidities. With average mentality and ready to cooperate

Exclusion criteria: Secondary hypothyroid patients, Newly diagnosed hypothyroid patients who started replacement therapy for less than 6 weeks, Other comorbidities.

Study tools:

Interviewing questionnaires including Complete history taking, Assessment of socioeconomic level (SES) using ElGilay et al.[9]: Socio-demographic score less than 50% (very low and low), score 50%- less than 75% (middle) and score 75% and more (high). **The Hypothyroidism-dependent quality of life (ThyDQoL):** It has with two overview items on present quality of life (present QoL) with scores ranged from excellent (3) to extremely bad (−3) and impact of hypothyroidism on quality of life in general (impact on QoL) that falls in the range from very much better (-3) to worse (1) without disease. The 18-item chief questionnaire evaluates disease impact on different life domains including work or sex life. For each domain, if applicable as the tool involves nine items that can be non-applicable, patients choose whether life in this domain would be very much better (−3) to worse (1) without disease. In addition, they rate the importance of the respective domain from very important (3) to not at all important (0). A weighted domain impact score is calculated by multiplying both ratings for each domain resulting in scores ranging from –9 (maximal negative impact of hypothyroidism on quality of life) to 3 (maximal positive impact of hypothyroidism). The 18-item ThyDQoL had very high internal consistency reliability (Cronbach's alpha = 0.949,

standardized item alpha = 0.95.[10] **The Thyroid Symptom Rating Questionnaire (ThySRQ) includes fifteen symptoms with**

Table (1) Comparison between the studied groups regarding QoL, satisfaction with life, symptom score and satisfaction with treatment:

Baseline data	Total
	N=257
Age (year):	
Mean ± SD	44.175±10.336
Gender:	
Female n (%)	172 (66.9)
SES:	
Very low and low	134 (52.1)
Middle	104 (40.5)
High	19 (7.4)
Marital status:	
Single	44 (17.1)
Married	171 (66.6)
Divorced/widow	42 (16.3)
BMI (kg/m^2):	
Mean ± SD	26.928±4.416
Duration (year):	
Median (min, max)	5 (0.5,12)
TSH:	
Uncontrolled (TSH>4.5)	68 (26.5)
Controlled (TSH from 2.5 - 4.5)	92 (35.8)
Strictly controlled (TSH<2.5)	97 (37.7)
T3/T4 ratio:	
Reduced	104 (40.5)
Average	153 (59.5)
Cause:	
Disease	157 (61.1)
Thyroidectomy	100 (38.9)

a 4-point symptom bother scale indicating how much the symptom bothers them from not at all, a little, quite a bit, very much (scoring 0, 1, 2, and 3, respectively) determining perceived severity of symptoms during the past 3 to 6 weeks. ThySRQ internal consistency reliability was unexpectedly high: Cronbach's alpha = 0.808, standardized alpha = 0.81.[10]

Thyroid treatment satisfaction-present questionnaire (The ThyTSQ-Present): It is seven-item questionnaire assessing satisfaction with treatment, and control of symptoms over the previous few weeks. Each questions response ranged from 6 to 0 (where 3 is considered a neutral option and 6 very satisfied). Higher scores mean higher satisfaction.[11] **Satisfaction with life questionnaire** (SWLS)**:** This five-item tool assesses the perceived satisfaction with life. [(12)] It includes a 7-point Likert scale ranging from: "1 = Strongly disagree" to "7 = Strongly agree". The possible range of scores is 5-35, with a score of 20 representing a neutral point on the scale and used as cutoff for evaluating satisfaction. The coefficient alpha for the scale has ranged from 0.79 to 0.89. [13]

All the interviewing questionnaire were translated using bi-lingual expert and tested via backward translation.

Clinical examination

Laboratory investigation: blood samples were withdrawn in the early morning to measure serum TSH, free T4 and free T3.

Operational design:

Field work: Patients who fulfilled inclusion criteria were interviewed during their visit to the clinic in the waiting room. The interview took 45 minutes to complete history taking, comprehensive clinical examination, answering the interviewing questionnaires. Then patient was sent to clinical pathology department for thyroid profile analysis. Result of thyroid profile was obtained by asking patient to send result to author or on scheduling next visit to clinic. The authors explained and helped illiterate patients to understand question to choose the appropriate answer in their point of view.

Statistical Analysis Data analysis was accomplished using the software SPSS (Statistical Package for the Social Sciences) version 20. Quantitative data was represented using means and standard deviations. Categorical variables were designated using their absolute frequencies, percentages and compared using chi square test. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were utilized to prove suppositions for use in parametric tests. Mann Whitney test (for not normally distributed data) was used to compare continuous variables between two groups. To compare non-parametric continuous variables between more than two groups, Kruskal Wallis test was used. P value <0.05 was considered statistically significant.

Table (2) Comparison between the studied groups regarding QoL, satisfaction with life, symptom score and satisfaction with treatment:

Parameter	Total	Groups			Test	p
		Uncontrolled	Controlled	Strictly controlled		
	N=257	N=68	N=92	N=97		
Present QoL: Median (min, max)	-2 (-3, 3)	2 (-3, 3)	1.5 (-3, 2)	-2 (-3, 3)	2.443◊	0.295
Thyroid-dependent QoL Median (min, max)	1(-3, 1)	0 (-3, 1)	1 (-3, 1)	0 (-3, 1)	2.685◊	0.261
Importance scale: Median (min, max)	0 (-6, 6)	0 (-6, 6)	0 (-6, 6)	0 (-6, 6)	2.569◊	0.277
ThyDQoL (18 item): Median (min, max)	0 (-9, 3)	-4 (-9, 3)	-6 (-9, 3)	-5 (-9, 3)	1.358◊	0.705
Thyroid treatment satisfaction: Median (min, max)	16 (5, 35)	11 (5, 21) ¥	19 (5, 32) ¥	22 (6, 35) ¥	73.23◊	<0.001*
Satisfaction (SWLS):						
Unsatisfied (<20)	155 60.3)	65 (95.6) ¥	45 (48.9)	45 (46.4)	48.198∞	<0.001*
Satisfied (>20)	102 (39.7)	3 (4.4)	47 (51.1)	52 (53.6)		
Thyroid symptoms scale Median (min, max)	10 (1, 40)	14 (4, 40) ¥	10 (3, 38)	8 (1,39)	11.578◊	0.003*

**p<0.05 is statistically significant ¥group responsible for significant difference on pairwise comparison ∞Chi square test ◊Kruskal Wallis test,.*

Administrative approval

The study was approved by manager of outpatient clinic and head of Internal Medicine department, faculty of medicine Zagazig University.

Ethical approval

An informed oral consent was obtained from all patients and confidentiality of data was assured. The study was approved by Ethical Committee of faculty of Medicine, Zagazig University.

Result

About 67% of patients were females and married. Mean age and BMI were 44.175 years and 26.928 kg/m^2. More than half of them had very low and low SES. Disease

duration ranged from 6 months to 12 years with median 5 years. Regarding TSH level, patients were divided into three **categories:** uncontrolled (TSH>4.5), controlled (TSH form 2.5 to 4.5) and strictly controlled (TSH<2.5) which represented 26.5%, 35.8% and 37.7% respectively. Concerning T3/T4 ratio, 40.5% of patients had reduced ratio (table 1).

Table (3) Relation between T3/T4 ratio, disease duration and outcome measures:

Parameter	T3/T4 ratio				Duration			
	Reduced	Average	Test	p	≤5 years	>5 years	Test	p
Present QoL: Median (min, max)	-1 (-3, 3)	2 (-3, 3)	-2.29¥	0.022*	-2 (-3, 3)	-2 (-3, 3)	-0.815¥	0.415
Thyroid-dependent QoL Median (min, max)	1 (-3, 1)	0 (-3, 1)	-1.51¥	0.131	1 (-3, 1)	0 (-3,1)	-2.468¥	0.014*
Importance scale: Median (min, max)	0(-6, 6)	0 (-6, 6)	-1.23¥	0.219	0.5 (-6,6)	0 (-6, 6)	-2.13¥	0.021*
ThyDQoL(18 item): Median (min, max)	-7 (-9, 3)	-4 (-9, 3)	-4.52¥	<0.001*	-4(-9, 3)	-6 (-9, 3)	-1.448¥	0.148
Thyroid treatment satisfaction: Median (min, max)	15 (6,35)	18 (5,33)	-2.13¥	0.033*	18 (5,35)	14 (5,33)	-1.939¥	0.053
Satisfaction (SWLS):								
Unsatisfied (<20)	66 (69.5)	89 (54.9)	5.286∞	0.022*	72 (54.5)	83 (66.4)	3.769∞	0.052
Satisfied (>20)	29 (30.5)	73 (45.1)			60 (45.5)	42 (33.6)		
Thyroid symptoms scale Median (min, max)	14 (2,40)	8 (1,40)	-4.32¥	<0.001*	10 (1,40)	9 (2, 39)	-0.301¥	0.763

**p<0.05 is statistically significant ¥Mann Whitney test ∞Chi square test*

Regarding satisfaction with life score, only 39.7% were satisfied. The patients reported scores denoting impaired quality of life, higher thyroid symptom scale, and lower treatment satisfaction scores respectively. There were statistically non-significant relation between level of control and QoL scores; present, hypothyroid dependent, importance rating or total thyrDol 18 scores. There was statistically significant relation between level of control and each of thyroid treatment satisfaction, satisfaction with life score and thyroid symptom scores. Regarding thyroid treatment satisfaction scores, on pairwise comparison, the difference is significant between each two groups with the strictly controlled group had the best score. The uncontrolled group had the worst SWLS (only 4.4% were satisfied) and the highest thyroid symptom score (Table 2).

There was statistically non-significant relation between level of control and thyroid-dependent QoL and importance rating scores. There was statistically significant relation between T3/T4 ratio and each of present, total thyrDol 18 (both scores were better in average ratio), thyroid treatment satisfaction, satisfaction with life score (all were higher in average ratio) and thyroid symptom scores (lower in those with average ratio) (Table 3).

There was statistically significant relation between level of control and thyroid-dependent QoL and importance rating

scores. There was statistically non-significant

Table (4) Relation between cause of primary hypothyroidism and outcome measures:

Parameter	Cause			
	Thyroiditis N=157	Thyroidectomy N=100	Test	p
Present QoL:				
Median (min, max)	1 (-3, 3)	2 (-3, 3)	-4.232¥	<0.001*
Thyroid-dependent QoL				
Median (min, max)	1 (-3, 1)	0 (-3, 1)	-3.495¥	<0.001*
Importance scale:				
Median (min, max)	0 (-6, 6)	2 (-6, 6)	-5.299¥	<0.001*
ThyDQoL(18 item):				
Median (min, max)	-7 (-9, 3)	-3 (-9, 3)	-5.722¥	<0.001*
Thyroid treatment satisfaction:				
Median (min, max)	15 (5, 35)	18 (5, 33)	-1.375¥	0.169
Satisfaction (SWLS):				
Unsatisfied (<20)	106 (67.5)	49 (49)		
Satisfied (>20)	51 (32.5)	51 (51)	8.75∞	0.002*
Thyroid symptoms scale				
Median (min, max)	10 (3, 40)	8.5 (1, 38)	-2.516¥	<0.012*

**p<0.05 is statistically significant ¥ Mann Whitney test ∞Chi square test*

relation between T3/T4 ratio and each of present, total thyrDol 18, thyroid treatment satisfaction, satisfaction with life score and thyroid symptom scores (Table 3).

Athyreotic patients had significantly better present QoL, 18-item thyDQoL and better importance rating scales and lower thyroid symptom scales than those with thyroiditis. More than half of them were satisfied with life versus only 32.5% among those with thyroiditis (Table 4).

Discussion

In the current study, QoL was impaired regardless TSH level. Even patients with TSH<2.5 did not report significantly better scores. Hence being biochemically euthyroid does not necessarily mean that the patients remain completely normal. QoL, SWLS, treatment satisfaction and symptoms score were significantly related to T3/T4 ratio, which was reduced in 40.5% of patients.

Average FT3/FT4 ratio was associated with better QoL scores, satisfaction with life and treatment and thyroid symptom scores. This finding points to importance of T3 level to control patient symptoms and improve well-being.

Hypothyroid patients on levothyroxine therapy who rendered biochemically euthyroid have demonstrated what appears to be residual impairment in QoL as reported in prior research.[14]

A previous study conveyed that using doses of thyroxine that were 50 mg higher than 'optimal' replacement was associated with better wellbeing scores.[15] However, there are not agreed upon guidelines that support such finding.

Reduced FT3/FT4 ratio represented approximately one third of patients on monotherapy in a prior study.[3]

The concept of tissue hypothyroidism, or hypothyroidism at the cellular level, is not a new emerging concept. It points to the

clinical paradox of symptoms, in spite of biochemical euthyroidism with "optimal" thyroxine dosage. Non-applicability of such concept in clinical field can be attributed to lack of an agreed upon, simple gold standard tool for this measurement[15] and that the current ATA guidelines recommend against using such tools except for research field.[2]

Lower TSH levels were associated with higher SWLS, lower symptom scores and higher satisfaction with treatment. This may point that high levothyroxine doses can combat lower T3 that made T3/T4 ratio around average values.

Molwwijk et al.[16] reported persistence of impaired QoL, reduced daily functioning, and residual symptoms, are common in patients in spite of replacement therapy and similar results were reported in prior research.[17-18]

In disharmony with the current finding, Winther et al.[19] reported that QoL of hypothyroid patients significantly improved after six months after levothyroxine therapy.

The finding agreed with an emerging revolution on traditional treatment of hypothyroidism. The conditional equilibrium formed between TSH and FT4 is called the set point, a narrow individual integrator of the stimulation of thyroid hormone production by TSH and negative feedback control of thyroid hormones upon TSH. The interlocking equilibrium of TSH and FT4 result in a kite-shaped distribution of the set points.[21] Unlike using a fixed TSH target for all patients, it renders the discriminatory TSH threshold between the euthyroid and hypothyroid state variable amongst the individuals in a population and, in an individual, conditionally dependent on paired FT4 concentrations or setpoints.[21-22]

Another regulatory component and chief provider to variation arises from TSH providing feed-forward stimulation of the enzymes deiodinase 1 and 2, regulating T4 to T3 conversion rates to genetically determined individual requirements.[23] This pathway is important in providing interpersonal T3 stability in thyroid health, rendering T3 generation to a significant extent independent of T4 supply. Nevertheless, the procedure fails in LT4-treated thyroidectomized patients, disturbing the balance between free FT3, FT4, and TSH accordingly, a certain TSH level attained in a healthy person cannot equally oblige as a treatment target for LT4 replacement after the patient has undergone thyroidectomy.[24]

A prior systematic review determined that higher circulating FT4 levels, not TSH levels, were linked to an amplified hazard of incident atrial fibrillation in euthyroids.[25]

Prospective research conducting on LT4-treated athyreotic patients with thyroid cancer found that patients with mildly suppressed TSH levels were closest to euthyroid, whereas TSH levels within the reference range were suggestive of tissue hypothyroidism in these patients.[26]

American Thyroid Association conducted a survey study that showed extensive dissatisfaction with standard monotherapy among patients or most thyroid specialists who prefer considered therapies alternative to LT4 treatment in hypothyroid patients.[27,28]

Awareness of being chronically ill with lifelong drug dependency could make patients unhappy and less healthy. Qualitative interview studies show that patients in general have a low understanding of their condition. When they experience hypothyroid symptoms at

initial diagnosis, the perception of disease susceptibility (and adherence to L-T4) is better, but patients who remain unwell despite a normal serum TSH felt that their normal result presented a barrier to further evaluation.[29]

Deteriorating QoL among patients with autoimmune thyroiditis than athyreotic ones in the current study agreed Watt and coauthors[30] with who concluded that autoimmunity, independent of thyroid function, impairs on QoL in patients with autoimmune hypothyroidism.

The study can be explained in context of some limitations; being cross-sectional study applied in single center. Yet the study had some strength points; all included patients received replacement dose at the same time. The tools used apart from SWLS were thyroid-specific so no need for adding control group and correlating QoL scores to laboratory parameters especially TSH, the hallmark in disease control. Thyroid antibodies were not measured.

We strongly recommend further large scale prospective clinical trials to reach an agreed-upon management strategy that helps hypothyroid patients to lead a healthy life not merely biochemical euthyroid.

Conclusion

Biochemical well-being not necessarily means physical wellbeing. TSH alone can render patients biochemically euthyroid yet the patients still suffer. Reduced T3/T4 ratio impaired QoL which pointed to importance of development of management starategy rather than relying only on TSH levels.

List of abbreviations*: TSH: thyroid stimulating hormone, FT3: free T3, FT4: free T4,*

Consent of publications:

All patients accepted to use their data for research purposes after ensuring confidentiality of their data.

Competing interest: The authors declared no conflict of interest

Funding: The author funded this research on their own.

Author contributions: all authors participated in preparation, writing of manuscript, and interviewing of patients.

Acknowledgement:

The authors acknowledged patients or their participation in this work

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