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Quality of Life in Patients with Biologically Controlled Primary Hypothyroidism: Assessment and Relationship with TSH Level

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Abstract

Some biologically well-controlled patients with primary hypothyroidism (PH) report persistent symptoms which can impact their quality of life (QoL). The aim of this study was to evaluate the QoL of patients with biologically controlled PH, and to determine the cutoff value of TSH associated with a better QoL.

Methods: This was a cross-sectional study including 70 adult patients with biologically controlled PH (TSH in the normal range). QoL was assessed by the SF36 questionnaire and treatment adherence was assessed by the Girerd questionnaire.

Results: The patients mean age was 51.2±9.6 years and the sex ratio (Men/Women) was 0.08. The mean duration of hypothyroidism was 8.4±6.7 years and the mean TSH level was 2.29±0.92mIU/L [0.62–4.25]. The mean value of the overall SF36 score was 61.11±23.8%. QoL was good in 53% of cases and impaired in 47% of cases. The altered items were related to physical state, perceived health, vitality, and psychological health. The TSH value at the time of the study was the only factor associated with impaired QoL (2.55±0.97 vs 2.05±0.80 mIU/L; p=0.024). A TSH>2.45mIU/L was the cutoff value associated with impaired QoL (p=0.015). After multivariate analysis, a TSH level > 2.45 mIU/L remained the only factor independently associated with impaired QoL.

Conclusions: Nearly half of patients with biologically controlled PH had impaired QoL. A TSH between 0.4 and 2.45 mUI/L is the target value to be achieved by the replacement therapy to improve the QoL of these patients.

Keywords: Hypothyroidism, Quality of life, Questionnaire, TSH, Treatment adherence

INTRODUCTION

Primary hypothyroidism (PH) is a chronic and frequent endocrine disorder with a prevalence ranging from 3.8 to 4.6% [1]. PH is defined by the inability of the thyroid gland to produce enough thyroid hormones. The

symptoms are numerous, nonspecific, and may vary from one patient to another. The main causes of PH include autoimmune and surgical conditions. The treatment involves hormonal replacement with L-thyroxine to relieve the symptoms and achieve a TSH level within the normal range. However, some well-controlled patients report persistent symptoms of hypothyroidism, which can impact their Quality of life (QoL).

The aim of this study was to:

- Assess the QoL of patients with biologically well-controlled primary hypothyroidism (TSH level within the normal range).
- Identify the sociodemographic, clinical, paraclinical, and therapeutic factors associated with an impaired QoL.
- Determine the cutoff value of TSH associated with a better QoL.

METHODS

We conducted a cross-sectional study involving the patients with PH who attended the Endocrinology department of La Rabta University Hospital (Tunis – Tunisia) during the month of December 2021. We included the patients with biologically controlled PH (TSH level between 0.5 and 4.5 mIU/L) aged between 18 and 65 years. Patients with central hypothyroidism, renal failure, liver failure, heart failure, evolutive cancer, chronic inflammation, or infection were not included.

Clinical and paraclinical data were collected through patient interviews, examination, and a review of medical records. Demographic information for each patient including age, gender, family history, medical history of hypertension, diabetes, dyslipidemia, autoimmune disease, lifestyle habits (smoking, alcoholism, physical exercise practice), socioeconomic status, and clinical history of PH (duration, etiology, treatment modalities), was recorded. A physical examination was conducted to assess weight, height, and identify any abnormalities in the thyroid gland. The TSH levels at diagnosis and recruitment, anti-thyroperoxidase (TPO) antibody levels at diagnosis, and the results of the thyroid ultrasound were recorded.

QoL was assessed for each patient using the short form survey questionnaire (SF-36) in its validated version in Tunisian dialect. It includes 36 questions assessing 8 items: physical functioning, role limitation due to physical health, vitality, emotional well-being, role limitation due to emotional health, social functioning, bodily pain, and general health perception. For each question, a higher score indicated a better QoL. An overall score was calculated as the sum of scores across the 8 items divided by eight. A score below 30 indicates a poor QoL, a score between 30 and 60 indicates a moderate QoL, and a score above 60 reflects good QoL. QoL was considered impaired when the score was below 60 [2].

Treatment adherence was assessed by the Girerd and Coll questionnaire in its validated version in Tunisian dialect [3]. It includes 6 “yes or no” questions. Patients were considered fully adherent if they gave 6 negative answers to the Girerd questionnaire, moderately adherent if they gave 1 or 2 positive answers to the questionnaire, and non-adherent if they gave 3 or more positive answers to the Girerd questionnaire.

Before collecting data, informed consent was obtained from each participant.

The study was approved by the Ethics Committee of La Rabta Hospital.

Sample size calculation:

The number of subjects needed (N) to assess the QoL of patients with biologically controlled PH was calculated based on the following formula:

$N= (Z^{\alpha}/2)^2 \times P0 \times (1- P0) / i^2$ ($Z^{\alpha}/2= 1.96$ for a

95% confidence level, P0= estimated prevalence of PH in general population, i= 0.05).

The highest estimated prevalence of PH in literature (4.6%) was used to calculate the sample size [1]. Thus, the minimum required sample size for the study was estimated at 67 patients.

Statistical analysis:

Data management and analysis were made using the Statistical Package for the Social Sciences (SPSS) version 26.0. We calculated frequencies and percentages for categorical variables and the mean ± standard deviation, medians, and quartiles for continuous variables. A student's t-test was used to compare 2 means, and ANOVA test was conducted to compare more than 2 means. The Chi-square test was used to compare percentages. Association of 2 continuous variables was analyzed by Spearman's correlation test. Cut-off values were determined by Receiver Operating Characteristic (ROC) curves. Factors associated with impaired QoL were identified by univariate and multivariate analysis. The multivariate analysis was conducted using binary logistic regression. Variables with a significance level below 20% in univariate analysis were included in the final model of the multivariate analysis. A p-value < 0.05 was considered statistically significant.

RESULTS:

Patients' characteristics:

The study included 70 patients. Table 1 presents patient characteristics.

Table 1: Characteristics of the study population

Parameter	Value
Age (years) , M ± SD [Min-Max]	51.2 ± 9.6 [23-65]
Sex Ratio (Men/Women)	0.08 (5/65)
Smoking, n (%)	3(4)
Sedentary lifestyle, n (%)	39 (56)
Socioeconomic status, n (%)	
Poor	35 (50)
Average	33 (47)
Good	2 (3)
Comorbidities, n (%)	
Diabetes	19 (27)
Hypertension	16 (23)
Dyslipidemia	14 (21)
Cardiovascular disease	4 (6)
Family History of thyroid disease, n (%)	23 (33)
Duration of PH (years), M ± SD [Min-Max]	8.4 ± 6.7 [0.5-30]
Etiologies of PH, n (%)	
Autoimmune	36 (51)
Thyroidectomy	15 (22)
Radioactive iodine therapy	10 (14)
Others	9 (13)
L-thyroxine dose (µg/day), M ± SD [Min-Max]	97.3 ± 39,1
Adherence to L-thyroxine treatment, n (%)	
Full adherent	51 (73)
Moderately adherent	19 (27)
Non-adherent	0 (0)
TSH level, M ± SD [Min-Max]	2.29 ± 0.92 [0 .62 – 4.25]

PH: Primary hypothyroidism; n: Number of patients; M: Mean; SD: Standard deviation; Min= Minimum; Max: Maximum

Quality of life assessment:

Table 2 shows the mean values of the overall score and each item of the SF-36 questionnaire.

The QoL was good in 53% of cases (n=37) and impaired in 47% of cases (n=33).

Table 2: Values of the overall score and each item of the SF-36 questionnaire

Item	Value M ± SD [Min – Max]	Perception
Overall score	61.1 ± 23.8 [13-97]	Good
Physical functioning	73.9 ± 20.6 [25-100]	Good
Role limitation due to physical health	56.8 ± 41.5 [0-100]	Moderate
Bodily pain and	61.5 ± 32.2 [10-100]	Good
General health perception	55.9 ± 23.3 [0-90]	Moderate
Vitality	53.4 ± 26.5 [0-95]	Moderate
Social functioning	69.8 ± 29.1 [0-100]	Good
Emotional well-being	58,4 ± 27,1 [16-100]	Moderate
Role limitation to emotional health	59,2 ± 42,6 [0-100]	Moderate

M: Mean ; SD: Standard deviation ; Min : minimum ; Max: maximum

Factors associated with impaired QoL

Table 3 compares the sociodemographic, clinical, paraclinical, and therapeutic data of the patients based on their QoL. The TSH level was the only factor significantly associated with an impaired QoL.

Table 3: Comparison of the sociodemographic, clinical, paraclinical, and therapeutic data of the patients based on their QoL

	Impaired QoL (n=33)	Good QoL (n=37)	P
Age (Years), M ±SD	51,6 ± 8,4	50,8 ± 10,7	0,751
Female gender, n (%)	33 (100)	32 (86)	0,056
Menopause, n (%)	23 (70)	19 (60)	0,416
Smoking, n (%)	1 (3)	2 (5)	1
Poor socioeconomic status, n (%)	19 (58)	16 (43)	0,338
Profession, n (%)	5 (15)	8 (22)	0,551
Sedentary lifestyle, n (%)	31 (94)	30 (81)	0,157
Family history of thyroid disease, n (%)	13 (39)	10 (27)	0,315
Comorbidities, n (%)	12	18	0,341
Duration of PH (years), M ± SD	8,2 ± 5,8	8,7 ± 7,5	0,806
Auto-immune PH, n (%)	15 (45)	19 (51)	0,628
Thyroidectomy, n (%)	6 (18)	9 (24)	0,566
Goiter, n (%)	9 (27)	4 (11)	0,345
BMI (Kg/m²), M ± SD	32 ± 6,06	29 ± 4,86	0,055
Obesity, n (%)	15 (45)	15 (40)	0,637
TSH at diagnosis (mUI/L), M ± SD	18,4 ± 20,2	25,1 ± 24,6	0,434
TSH at recruitment (mUI/L), M ± SD	2,6 ± 1	2,1 ± 0,8	0,024
Positive TPO antibodies, n (%)	6 (18)	2 (5)	0,431
Abnormality in thyroid ultrasound, n (%)	19 (58)	15 (41)	1
L-Thyroxine dose (µg/day), M ± SD	102,27 ± 40,19	92,9 ± 38,02	0,320
Moderate adherence to treatment, N (%)	7 (21)	12 (32)	0,420

QoL : Quality of life ; M : Mean ; SD : Standard deviation ; N : Number of patients ; BMI: Body mass index; PH: Primary hypothyroidism

A TSH level< 2.45 mUI/l was associated with a better QoL with a sensitivity of 61%, a specificity of 70%, and an area under the curve (AUC) equal to 0.666 as shown in Figure 1 (p= 0.024). Figure 2 shows the median values and quartiles of SF-36 overall scores based on a TSH level < 2.45 mUI/l (p=0.046).

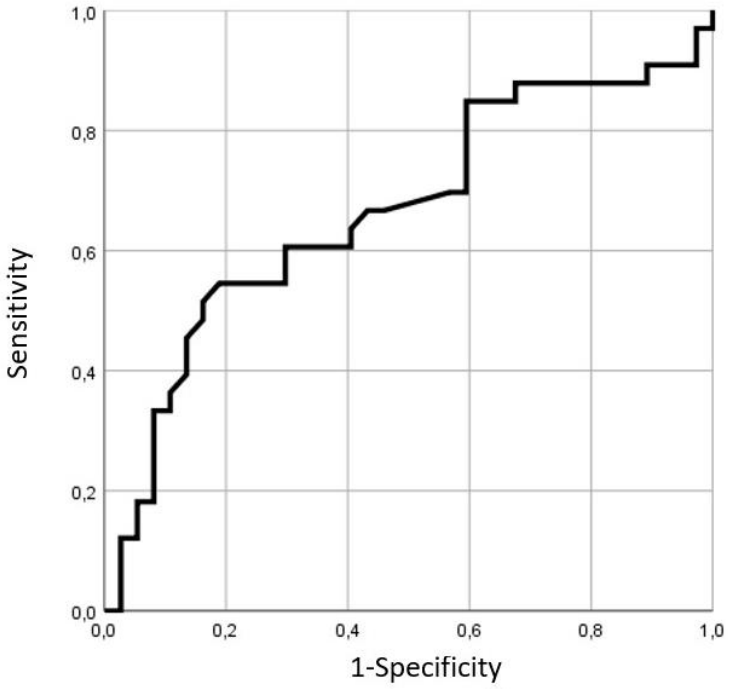

Figure 1: ROC curve assessing TSH level according to quality of life

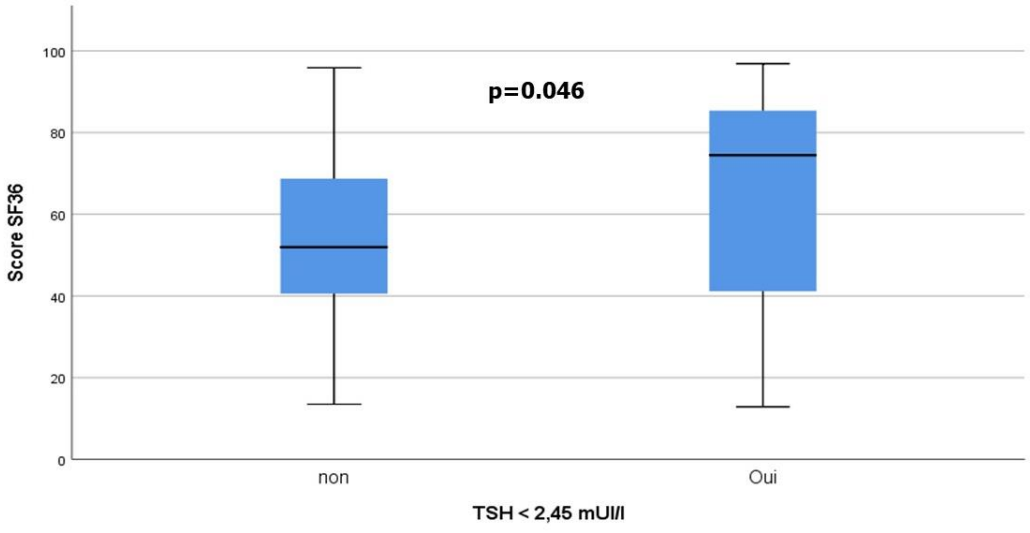

Figure 2: Box plot representing the medians and quartiles of the SF36 Score based on a TSH level < 2.45 mIU/L

There was no correlation between the SF36 overall score and the TSH level (r= -0.203, p= 0.108). There was no correlation between the SF36 overall score and the anti-TPO antibody levels (r= -0.047, p= 0.092).

In multivariate analysis, which included in addition to a TSH level >2.45mUI/l, female gender, sedentary lifestyle, and BMI> 30.5 Kg/m², a TSH level >2.45 mUI/l remained significantly associated with impaired QoL (p= 0.04, adjusted OR [CI 95%] = 3.7 [1.1-13.3]).

DISCUSSION

Numerous studies have assessed the QoL in patients with PH, but only a limited number have focused on those with biologically well-controlled PH. Various questionnaires have been utilized for this purpose. Some are specific to thyroid diseases, such as Underactive Thyroid-Dependent Quality of Life (ThyDQoL), Thyroid-Specific Patient-Reported Outcome Measure (ThyPRO), and Hypothyroid-Specific Health-Related Quality of Life Questionnaire (HRQL), while others were nonspecific, like the SF-36, the General Health Questionnaire 12-items (GHQ-12) [4-12,15,16].

In the present study, the SF-36 questionnaire was used due to the availability of a validated version in Tunisian dialect. This questionnaire was also selected as it comprehensively evaluates both the physical and mental aspects of health. We found that QoL was impaired in 47% of cases. Items specially impaired were role limitation due to physical health, vitality, mental health, and general health perception. Our results are consistent with those found by other authors. In their study, Kelderman-Bolk et al. evaluated the QoL in patients with stable doses of L-Thyroxine for PH using the SF-36 questionnaire, Hospital Anxiety and Depression Scale, and Multidimensional Fatigue Index 20. They observed that QoL was impaired on all scales compared to a reference population [4]. Similarly, Al Quran et al., utilizing the ThyPRO scale, demonstrated that all domains of the questionnaire were affected in all the patients, with notable impacts on fatigue, emotional susceptibility, and anxiety [5].

Factors associated with impaired QoL in patients with biologically well-controlled primary hypothyroidism:

Sociodemographic and clinical factors were not associated with QoL in our study. In the study by Guatj et al., an age exceeding 50 years old, and in the study by Djurovic et al., an age between 60 and 75 years old, were both associated with poorer QoL [6,7]. Other sociodemographic and clinical factors, such as female gender [8], physical activity [9] and comorbidities [4,5] may influence the QoL of patients with PH.

In our study, only the TSH level at recruitment showed a significant association with QoL. Indeed, TSH levels were higher in patients with impaired QoL, and a TSH level> 2.45 mUI/l remained associated with poor QoL even after multivariate analysis. These results were in agreement with the findings of Moron Diaz et al. who noted that in adequately treated hypothyroidism with TSH levels within the normal laboratory ranges, a lower TSH value was associated with better QoL [10]. Nevertheless, Walsh et al. and Kelderman-Bolk et al. found that a TSH value within the lower limit of the reference range was not associated with a better QoL [4,11]. Furthermore, Mithal et al. observed that the mean SF-36 Physical Health and Mental Health scores were worse among patients with a TSH level > 4 mUI/L (undertreated patients) and < 0.40 mUI/L (overtreated patients) when compared to

patients with a normal TSH level [12].

Having a better QoL when TSH levels are lower may be explained by the inter-individual variability of TSH levels and the fact that baseline TSH values are genetically determined and fluctuate around an endogen set-point unique to each person. As a consequence, the reference range for TSH level in the general population is not applicable to certain persons who have a baseline TSH value prior to the onset of PH, lower than general population [13,14].

TPO antibody levels were not correlated to QoL in our study. However, Ott et al. and Djurovic et al. demonstrated that positive and high TPO antibody levels were associated with impaired QoL [7,15]. On the other hand, Watt et al. confirmed this association even when TSH and FT4 levels were not found to be related to QoL [16]. Hence, the presence of positive TPO antibodies may negatively impact QoL irrespective of thyroid function. This could be attributed to micro-vascular alterations seen in autoimmune diseases, which may potentially occur in the central nervous system [17].

In our study, all patients were receiving L-thyroxine alone. Some studies have suggested a benefit from combined thyroxine (T4) and triiodothyronine (T3) treatment in patients with PH and persistent symptoms of hypothyroidism [18]. However, the impact of this therapeutic approach on QoL remains controversial [11, 19].

Limitations

The main limitations of the study were the small sample size and the absence of a control group. Studies involving larger samples are needed to validate the TSH threshold associated with better QoL.

CONCLUSION

Nearly half of the patients with biologically well-controlled PH had impaired QoL. We recommend assessing the QoL in patients treated with L-thyroxine, even when the TSH level is within the normal range. In non-elderly subjects and in the absence of heart disease, we suggest targeting a TSH level between 0.4 and 2.45 mIU/L through hormonal replacement therapy in order to improve the QoL of these patients.

Conflict of interest: none.

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جودة الحياة لدى المرضى بقصور الغدة الدرقية المتحكّم فيه بيولوجيًا: التقييم والعلاقة بمستوى الثيروتروبين

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الملخص

الخلفية والاهداف : المرضى الذين يعانون من قصور الغدة الدرقية الأولي المسيطر عليه بيولوجيًا يبلغون عن أعراض مستمرة يمكن أن تؤثر على جودة حياتهم

الهدف من هذه الدراسة هو تقييم جودة الحياة للمرضى الذين يعانون من قصور الغدة الدرقية المسيطر عليه بيولوجيًا، وتحديد القيمة القاطعة لمستوى هرمون الغدة الدرقية(الثيروتروبين) المرتبطة بجودة حياة أفضل

منهجية الدراسة: دراسة مستعرضة شملت 70 مريضًا بالغًا يعانون من قصور الغدة الدرقية المسيطر عليه بيولوجيًا تم تقييم جودة الحياة وتقييم الالتزام بالعلاج

النتائج: كان متوسط عمر المرضى 9.6±51.2 عامًا ونسبة الجنس (الذكور/الإناث) 0.08 كان متوسط مدة قصور الغدة الدرقية 6.7±8.4 سنوات وكان متوسط مستوى الثيروتروبين ميلي وحدة دولية/لتر [0.62–4.25]. 0.92±2.29 كان متوسط قيمة الدرجة الإجمالية لاستبيان جودة الحياة 23.8±61.11%. كانت جودة الحياة جيدة في 53% من الحالات ومتعكرة في 47% من الحالات. كانت العناصر المتأثرة مرتبطة بالحالة البدنية، والصحة المتصورة، والنشاط، والصحة النفسية. كان مستوى الثيروتروبين في وقت الدراسة هو العامل الوحيد المرتبط بتدهور جودة الحياة (0.97±2.55 مقابل 0.80±2.05 ميلي وحدة دولية/لتر؛ پ=0.024). مستوى ثيروتروبين <2.65 ميلي وحدة دولية/لتر هو القيمة القاطعة المرتبطة بتدهور جودة الحياة (پ=0.015)

بعد تحليل متعدد المتغيرات، ظل مستوى ثيروتروبين <2.45 ميلي وحدة دولية/لتر هو العامل الوحيد المرتبط بشكل مستقل بتدهور جودة الحياة

الاستنتاجات : حوالي نصف المرضى الذين يعانون من قصور الغدة الدرقية المسيطر عليه بيولوجيًا لديهم جودة حياة متدهورة مستوى ثيروتروبين بين 0.4 و2.45 ميلي وحدة دولية/لتر هو الهدف الذي يجب تحقيقه بواسطة العلاج البديل لتحسين جودة حياة هؤلاء المرضى

الكلمات الدالة: قصور الغدة الدرقية، جودة الحياة، استبيان، ثيروتروبين، الالتزام بالعلاج.