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ORIGINAL ARTICLE

Correlation between TSH levels and quality of life among subjects with well-controlled primary hypothyroidism

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Abstract

Purpose It has been suggested that increasing levothyroxine dose to lower TSH levels within the normal laboratory range might be a therapeutic option for patients with apparently well-controlled primary hypothyroidism who are dissatisfied with their treatment and complain of physical or psychological symptoms. This study assessed whether there is a relationship between TSH levels and health-related quality of life (HRQoL) among subjects with adequately treated hypothyroidism.

Methods HRQoL was measured with the specific thyroid disease ThyPRO-39 questionnaire in 218 consecutive patients with primary hypothyroidism of any cause attending an Endocrinology Department in a single center. Patients had TSH values within the normal laboratory range on a blood test performed not before than 6 weeks prior to study participation, but they were not aware of their lab results. The association between TSH values and the different ThyPRO-39 scales was analyzed by means of multiple regression models, both linear and additive, in which, in addition to TSH, a wide set of clinical and sociodemographic variables potentially related to HRQoL were also considered.

Results TSH levels and the use of anxiolytic and antidepressant drugs were the only variables that showed a positive linear correlation with the ThyPRO-39 composite scale in the multivariate regression analysis, indicating greater impairment in HRQoL with increasing TSH values. TSH was also independently correlated to scores of scales dealing on tiredness and emotional susceptibility.

Conclusions In patients with primary hypothyroidism, higher TSH values, even within the normal reference range, are associated with greater deterioration of HRQoL.

Keywords Hypothyroidism · Quality of life · Patient-reported outcome · Levothyroxine · TSH

Introduction

Primary hypothyroidism is a common endocrine disease. According to a recent national epidemiological survey, 7.1% of women and 1.2% of men of adult age have a diagnosis of hypothyroidism in Spain [1]. Treatment is considered to be relatively simple, and consists of the administration of substitutive replacement with levothyroxine, in order to resolve symptoms and achieve a TSH level within the laboratory normal range. However, it is well known that some patients with biochemically well-controlled hypothyroidism express dissatisfaction with their treatment and continue to have significant impairment in their quality of life [2–5]. The reason for this phenomenon is unknown. A greater probability to diagnose hypothyroidism among subjects with poor baseline health-related quality of life, increased prevalence of non-thyroid comorbidities, detrimental effects on the quality of life of thyroid

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autoimmunity itself or simply awareness of suffering a chronic disease, have been all proposed as potential causes [6–8]. However, issues related to inadequacy of medical treatment have received greater attention. For one hand, it has been hypothesized that levothyroxine could not be able to restore normal concentrations of triiodothyronine, the active hormone, in all target tissues. Generation of triiodothyronine in subjects with hypothyroidism entirely depends on peripheral deiodination from thyroxine and this pathway alone could be not sufficient to fully restore daily triiodothyronine production during levothyroxine therapy [7, 9]. However, although some individual studies have found positive effects for the coadministration of levothyroxine and liothyronine [10], combination therapy has not been shown to be superior to the conventional treatment with levothyroxine alone on well-being, cognitive function, or quality of life [11]. Second, in the last decade a debate has arisen about the need to lower the upper normal limit of TSH levels, as the distribution of TSH values in the general population is skewed to the right, mainly because of higher TSH concentrations among subjects with occult autoimmune thyroid disease [12, 13]. In light of this controversy, some authors have suggested that, in patients who persist symptomatic with TSH levels within the upper part of the normal range, it would be reasonable to titrate levothyroxine in order to bring TSH to the lower part of the reference values [13, 14]. However, scientific evidence to support this approach is lacking. Two double-blind, randomized clinical studies [15, 16] analyzed the effect of levothyroxine dose titration, resulting in different ranges of TSH within the normal reference values, and lower TSH values were not associated with higher measures of well-being, quality of life, mood, or cognitive function. However, and although not recommended by clinical practice guidelines [11], some authorities have defended the use of a TSH target in the lower half of the normal range for treatment of patients with primary hypothyroidism [17, 18], a view that seems to be shared precisely by more expert thyroidologists, who tend to prefer lower TSH goals, at least for symptomatic or young patients [19, 20]. Even more, some data suggest that treating general practitioners are open to increase levothyroxine doses in order to make patients feel better as long as TSH levels remain within the normal range [21]. This demonstrates that there is still a perceived clinical benefit to maintain TSH levels in the lower part of the normal reference limit in the follow-up of patients with hypothyroidism, thus indicating that further research on this field is needed. Accordingly, the present study was aimed to assess the relationship between TSH levels and patient-reported outcomes, assessed with a specific thyroid-disease instrument to measure health-related quality of life, among adult patients with well-controlled primary hypothyroidism.

Material and methods

Subjects

Adult patients (18–75 years) with primary hypothyroidism of any cause (spontaneous or iatrogenic) attending the Endocrinology Department of a single center in Spain were consecutively included. Patients with low-risk differentiated thyroid carcinoma were also invited to participate, as long as they were free of disease and had not received any treatment directed to their neoplastic pathology (surgery or radioiodine) for a minimum period of 5 years. Two additional inclusion criteria were required: (i) being on the same dose of levothyroxine for a period of time not <3 months, and (ii) having a TSH level within the normal range for the hospital's laboratory in a blood test performed no longer than 6 weeks before participation. Exclusion criteria included: inability to read and understand Spanish language, cancer (except differentiated thyroid cancer with the characteristics mentioned above), pregnancy or puerperium, cognitive impairment, psychotic diseases, and recent stressful life event. Considered stressful life events included those related to personal health (i.e., serious physical illness or injury) as well as social, familial, or personal stressors (i.e., death or serious disease of a family member, job conflicts, financial problems, etc.) causing a severe negative impact on psychological status.

On the whole, 223 patients were invited to participate, although five of them were further excluded as, in the opinion of the enrolling researchers, they had experienced a significant recent stressful life event. Thus, the final study population was composed of 218 patients.

Study procedures

Subjects were recruited when they attended a scheduled visit to follow-up of their thyroid disease. Clinical and sociodemographic data were recorded of each participant. Health-related quality of life was evaluated with the Spanish version of the short-form of the Thyroid-Specific Quality of Life Patient-Reported Outcome (ThyPRO-39) questionnaire [22]. The questionnaire consists of 39 items, summarized in twelve scales, four of them covering physical symptoms (symptoms related to goiter, hyperthyroidism, hypothyroidism, and eyes, respectively), two focusing on mental symptoms (anxiety and depressivity), three on functionality and well-being (tiredness, cognition, and emotional susceptibility), and three on participation and social function (impaired social life, impaired daily life, and cosmetic complaints), as well as a single item measuring overall impact of thyroid disease on quality of life. The items are scored from 0 to 5, following a Likert scale (where "0" is equivalent to "nothing at all" and "5" to "very much"),

always considering the patient's perception during the last 4 weeks. The average score of items in each scale is divided by four and multiplied by 100 to yield scales from 0 to 100. In addition, a ThyPRO composite score, based on 21 items from the tiredness, cognition, anxiety, depressivity, emotional susceptibility, impaired social life, and impaired daily life scales, plus the overall quality of life item, was also computed. The usual practice in our center is for patients to have a blood test done a few days before their appointment. Those who took part in the study filled out the ThyPRO-39 questionnaire before entering the medical practice, without being aware of their TSH results. Serum levels of TSH were measured in the Biochemistry Laboratory of the Insular University Hospital, using a two-site immunoenzymatic ("sandwich") assay (Beckman Coulter, France) (normal range: 0.38–5.33 mU/l).

Written consent was obtained from each patient after full explanation of the purpose and nature of all procedures used. The study was approved by the Ethics Committee of the Complejo Hospitalario Universitario Insular Materno-Infantil.

Statistical analyses

Categorical variables are expressed as frequencies and continuous variables as medians and interquartile ranges (25th–75th percentile). The crude association of each scale of the questionnaire with TSH was evaluated by means of Spearman correlations. In addition, multiple regression models were performed in which each of the ThyPRO scales were considered as dependent variables. Age, sex, primary thyroid disease, TSH level, body mass index (BMI), current levothyroxine dose (μg/kg/day), smoking, number of non-thyroid comorbidities, previous diagnosis of depression, current use of anxiolytic or antidepressant medications, education level, and living arrangement were fit as independent variables. Categorical variables with multiple levels were combined for analyses: primary thyroid disease was coded as "spontaneous or iatrogenic hypothyroidism secondary to autoimmune diseases" (Hashimoto's disease and Graves' disease with or without orbitopathy), "iatrogenic hypothyroidism secondary to non-autoimmune disorders" (toxic or nontoxic nodular thyroid disease), and "thyroid cancer"; number of comorbidities was coded as "none", "one", and "two or more"; education level was coded as "primary education or lower" and "secondary education or higher"; and living arrangement was coded as "living alone" or "other". First, a selection of variables was carried out using the best subset regression and the Bayesian information criteria. The eventual non-linear effects of the continuous variables were explored by additive regression [23]. The estimated models were summarized, as appropriate, as coefficients, standard errors or cubic splines when the effect was nonlinear. The degree of smoothing of the splines is given by the effective degree-of-freedom, this parameter being 1 when the fit is linear. Statistical significance was set at $P < 0.05$. Data were analyzed using the R package, version 3.6.1 [24].

Table 1 Clinical and sociodemographic characteristics of the population

Age (years)	54 (45–62)
Female sex (%)	85.8
Primary thyroid disease	
Spontaneous or iatrogenic hypothyroidism secondary to autoimmune diseases (%)	71.9
Hashimoto's disease (%)	57.1
Graves' disease without orbitopathy (%)	11.1
Graves' disease with orbitopathy (%)	3.7
Iatrogenic hypothyroidism secondary to non-autoimmune thyroid diseases (%)	16.2
Nontoxic goiter (%)	13.4
Toxic goiter (%)	2.3
Hypothyroidism secondary to external radiotherapy (%)	0.5
Thyroid cancer (%)	11.9
TSH (mU/l)	1.90 (1.08–3.19)
Body mass index (kg/m^2)	27.9 (25.0–31.9)
Current levothyroxine dose (μg/kg/day)	1.28 (1.00–1.66)
Smoking	
Nonsmoker (%)	61.6
Previous smoker (%)	27.3
Smoker (%)	17.9
Number of non-thyroid comorbidities	
None (%)	49.5
One (%)	40.4
Two or more (%)	10.1
Previous diagnosis of depression (%)	17.9
Current use of anxiolytic and/or antidepressant drugs (%)	25.2
Education level	
Primary education or lower (%)	41.7
Secondary education or higher (%)	58.3
Living arrangement	
Living alone (%)	11.9
Other (%)	88.1

Data are percentages or medians (interquartile ranges)

Results

The clinical and demographic characteristics of the study population are shown in Table 1. As expected, most of the participants were women. All patients were receiving levothyroxine as the only treatment for hypothyroidism.

Table 2 Scores of the ThyPRO-39 questionnaire in the study population and bivariate correlations between scales and TSH values

	Score	*r*	*P*
Goiter symptoms	0 (0–16.7)	−0.038	0.58
Hyperthyroid symptoms	18.8 (6.2–37.5)	−0.068	0.32
Hypothyroid symptoms	25 (12.5–43.8)	0.043	0.53
Eye symptoms	25 (8.3–50)	0.015	0.83
Tiredness	50 (25–67)	0.140	0.041
Cognitive complaints	25 (8.3–50)	−0.0086	0.90
Anxiety	25 (8.3–50)	0.077	0.26
Depressivity	25 (16.7–58.3)	0.042	0.54
Emotional susceptibility	35.4 (25–58.3)	0.110	0.13
Impaired social life	0 (0–16.7)	−0.024	0.73
Impaired daily life	8.3 (0–25)	0.064	0.35
Cosmetic complaints	8.3 (0–25)	0.033	0.63
Overall quality of life impact	25 (0–50)	0.095	0.17
Composite scale	26.1 (14.8–42.3)	0.083	0.22

Scores are presented as medians (interquartile ranges)

Autoimmune thyroid diseases, in particular Hashimoto's thyroiditis, were the most common cause of hypothyroidism. The distribution of TSH levels was right skewed, so that 70% of the subjects had TSH levels within the lower half of the normal laboratory range. It was noteworthy that a high proportion of patients had a history of affective disorders: 17.9% had been diagnosed and treated for depression at some point in their lives, 13.8% were currently taking antidepressant drugs, 7.3% were taking anxiolytics, and 4.1% were taking both types of medications. Table 1 in the Supplementary Material shows the results of the ThyPRO-39 among patients who were or were not taking antidepressant and/or anxyolitic drugs. Scores on all the questionnaire scales, except the one dealing on eye symptoms, were significantly worse among the subgroup of participants who were on psychotropic medications. Table 2 shows the scale scores and the linear bivariate correlations between each scale and TSH values on the whole study population. Positive Spearman coefficients were found for scales dealing on hypothyroid symptoms, eye symptoms, tiredness, anxiety, depressivity, emotional susceptibility, and daily life, as well as for the individual item assessing the global impact of thyroid disease on health-related quality of life and for the composite scale, but the strength of the correlation only was statistically significant for the tiredness scale. However, in multiple regression analyses, TSH was significantly associated with tiredness, emotional susceptibility, and composite scales. Additive regression models did not identify nonlinear effects of TSH on any of the three scales. Regarding to the rest of the assessed covariates, all the scales of the questionnaire, except the scale related to eye symptoms, were associated with the current taking of anxiolytic and/or antidepressant medications. Female sex was associated with hypothyroid symptoms, tiredness, and emotional susceptibility, and a greater number of non-thyroid comorbidities was associated with tiredness, emotional susceptibility, and impaired social life. Complete results of the multiple regression models are shown in Table 3. The nonlinear effects detected in the generalized additive models are depicted in Fig. 1. BMI showed nonlinear associations with the symptoms of hyperthyroidism, tiredness, and cosmetic complaints, with a sharp increase in score levels from BMI values around 25–27 kg/m^2. Emotional susceptibility decreased with the age, but this relationship was also not linear, and became less pronounced from about age 45 (Fig. 1c).

Discussion

This is the first study aimed to assess the relationship between serum levels of TSH and health-related quality of life in patients adequately treated for primary hypothyroidism, specifically using a validated thyroid-disease instrument to measure patient-reported outcomes. As main finding, a positive correlation was found between TSH values and a composite scale that summarizes the seven mental and social well-being and function scales of the ThyPRO-39 questionnaire, becoming a comprehensive measure of thyroid disease-related quality of life. In addition, TSH was also positively correlated to the scores of scales that measure tiredness and emotional susceptibility, indicating a particularly greater impairment of both aspects of quality of life with increasing TSH levels. It was noteworthy that scales measuring these two dimensions of quality of life were more strongly correlated to TSH than the scale specifically designed to assess symptoms of hypothyroidism. However, this finding was probably reassuring. In a previous study performed on patients with untreated hypothyroidism secondary to chronic autoimmune thyroiditis [5], the tiredness an emotional susceptibility scales of the ThyPRO were just those whose scores showed a greater improvement with levothyroxine therapy, thus indicating that they are sensitive markers of the patient's perception of treatment benefit.

On the whole, the correlation between TSH levels and certain outcomes reported by the patients, particularly those related to fatigue perception and emotional susceptibility, suggests that it does exist an association between the effects of levothyroxine replacement therapy and patient's quality of life. Previously, Saravanan et al. [25] also observed a positive correlation between serum concentrations of TSH and impaired psychological well-being, measured with the General Health Questionnaire-12, on 473 hypothyroid subjects on levothyroxine replacement with TSH levels

Table 3 Multivariate regression analyses of variables independently associated with different scales of the ThyPRO-39

Scale	Coefficient	*P*
Goiter symptoms		
(Intercept)	8.602 (1.325)	<0.001
Current use of anxiolytics/antidepressants	9.045 (2.663)	<0.001
Hyperthyroid symptoms		
(Intercept)	21.133 (1.747)	<0.001
Living alone	−11.169 (4.617)	0.016
Current use of anxiolytics/antidepressants	14.198 (3.372)	<0.001
Body mass index	Nonlinear (EDF = 1.63)	0.030
Hypothyroid symptoms		
(Intercept)	14.358 (4.166)	<0.001
Female sex	15.227 (4.491)	<0.001
Current use of anxiolytics/antidepressants	8.405 (3.597)	0.02
Eye symptoms		
(Intercept)	7.617 (8.003)	0.342
Age, per year	0.420 (0.146)	0.004
Tiredness		
(Intercept)	22.785 (5.636)	<0.001
TSH, per mU/l	3.725 (1.275)	0.004
Female sex	10.139 (4.955)	0.042
Current use of anxiolytics/antidepressants	15.091 (4.130)	<0.001
Number of comorbidities	6.070 (2.310)	0.009
Body mass index	Nonlinear (EDF = 2.46)	0.020
Cognitive complaints		
(Intercept)	26.515 (2.093)	<0.001
Current use of anxiolytics/antidepressants	19.959 (4.166)	<0.001
Anxiety		
(Intercept)	27.435 (2.154)	<0.001
Current use of anxiolytics/antidepressants	20.232 (4.350)	<0.001
Depressivity		
(Intercept)	28.193 (1.938)	<0.001
Current use of anxiolytics/antidepressants	27.079 (3.944)	<0.001
Emotional susceptibility		
(Intercept)	−2.554 (9.598)	0.790
TSH, per mU/l	2.730 (1.156)	0.019
Female sex	10.726 (4.471)	0.017
Body mass index, per kg/m^2	0.743 (0.283)	0.009
Current use of anxiolytics/antidepressants	22.945 (3.807)	<0.001
Number of comorbidities	5.408 (2.129)	0.012
Age	Nonlinear (EDF = 1.81)	0.006
Impaired social life		
(Intercept)	3.756 (1.611)	0.021
Current use of anxiolytics/antidepressants	14.279 (2.700)	<0.001
Number of comorbidities	4.574 (1.518)	0.003
Impaired daily life		
(Intercept)	11.715 (1.738)	<0.001
Current use of anxiolytics/antidepressants	20.035 (3.511)	<0.001
Cosmetic complaints		
(Intercept)	15.731 (1.589)	<0.001
Current use of anxiolytics/antidepressants	7.846 (3.218)	0.016
Body mass index	Nonlinear (EDF = 2.61)	0.006
Overall quality of life impact	25 (0–50)	0.095
(Intercept)	11.508 (4.038)	0.005
Current use of anxiolytics/antidepressants	11.964 (4.713)	0.012
Autoimmune thyroid diseases	11.919 (4.574)	0.010
Composite scale	26.1 (14.8–42.3)	0.083
(Intercept)	20.130 (2.596)	<0.001
TSH, per mU/L	2.240 (0.931)	0.017
Current use of anxiolytics/antidepressants	20.430 (2.924)	<0.001

Correlation coefficients are given for linear associations. Nonlinear associations were modeled using cubic splines (see Fig. 1). The degree of smoothing of the splines is given by the effective degree-of-freedom (EDF)

Variable selection was performed using the best subset regression method and Bayesian information criteria (BIC)

within the normal laboratory reference. The present investigation, which was performed with the ThyPRO, probably the best specific tool to assess health-related quality of life in patients with thyroid diseases [26], reinforces those findings. In addition, we adjusted for the effect of different clinical and social variables that could potentially impact on patient's quality of life, particularly the coexistence of anxiety and depression disorders, which were strongly associated with virtually all scales of the ThyPRO questionnaire in our population. In our study, the relationship between TSH levels and quality of life only became apparent when applying multivariate models that included the concomitant use of anxiolytics and/or antidepressants drugs. Previously, depression has been found to be positively correlated to TSH values in population on levothyroxine treatment [27]. Therefore, this point becomes particularly relevant, given that a quarter of our study population was taking antidepressant and/or anxiolytic drugs. This should be viewed in the context of the high consumption of psychotropic medications in Spain. According to data from the 2012 National Health Survey, 19.3% of women and 8.5% of men between 45 and 64 years of age consumed antidepressant and anxiolytic drugs in Spain [28]. Higher rates would even be expected among subjects with hypothyroidism, who have a higher prevalence of depression and anxiety than the general population and make greater use of these types of medications [29, 30].

Other studies on subjects with treated hypothyroidism have failed to show association between quality of life and TSH levels within the normal range, but their sample size was probably too small to get statistical power [5] or TSH was only considered as a dichotomic variable, and not as a continuous variable [4, 31]. In this regard, it should be noted that our statistical analysis, using generalized additive models, could not identify any threshold above which the rise in TSH values resulted in a greater impact on quality of life measurements.

This study, however, is contrary to the results of two randomized clinical trials [15, 16] that evaluated the effect of fine titration of levothyroxine, resulting in different TSH values within the normal range, none of which could demonstrate benefits of lower values of TSH on the physical well-being, cognition, or mood of hypothyroid patients. There are several explanations for this contradiction. First, the sample size of both clinical trials was small, with few participants in each group with a different range for TSH. Second, patients were not selected on the basis of symptoms status or impaired quality of life. It should be taken into account that only a relatively small proportion of patients with hypothyroidism remain symptomatic or dissatisfied with their treatment [11]. Ideally, this subgroup of patients would constitute the most appropriate target population on

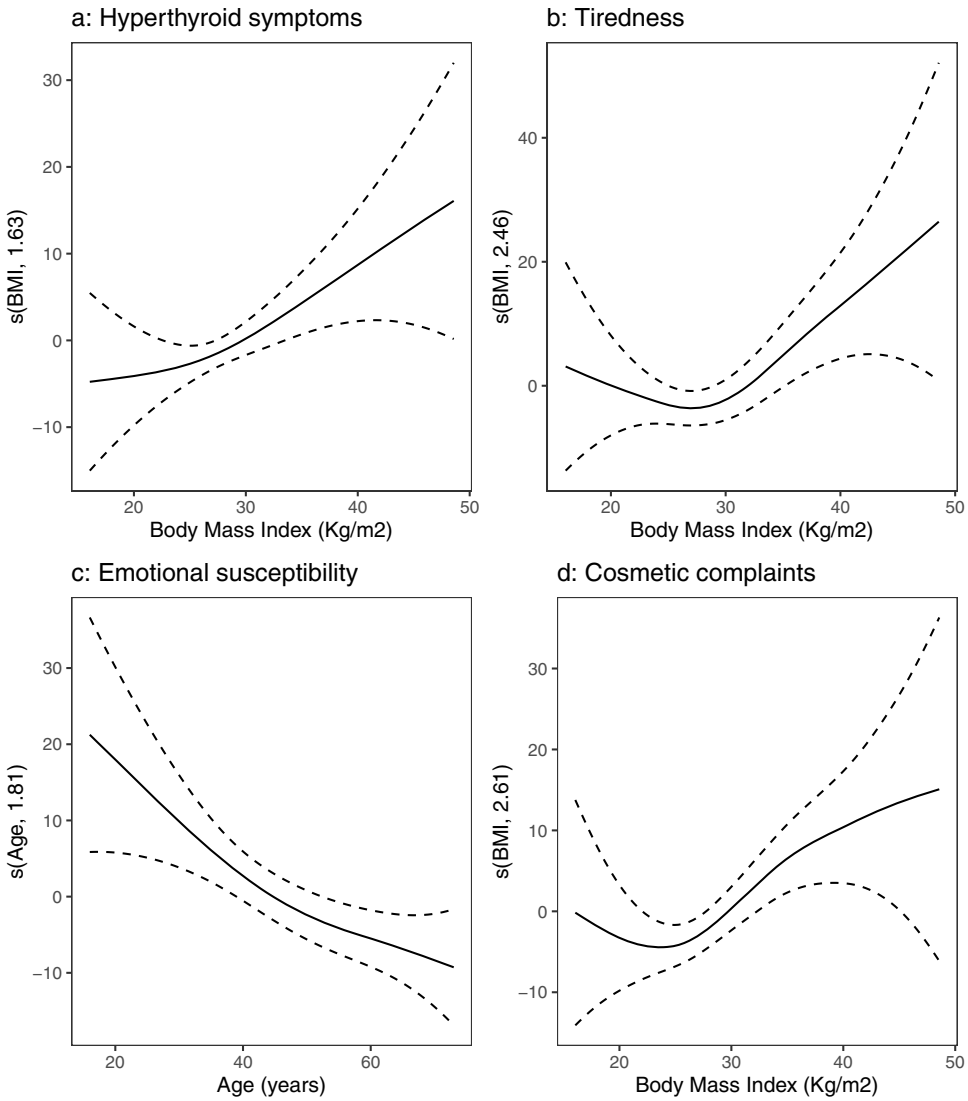

Fig. 1 Effects of body mass index and age on different ThyPRO-39 scales. The nonlinear effect of the *X*-axis variables is plotted on the *Y*-axis. The number between brackets denotes the effective degree of freedom, this parameter being 1 when the fit is linear

which to conduct a clinical trial to assess the effect of levothyroxine dose adjustment on health-related quality of life. In fact, a small open uncontrolled study on 23 patients with hypothyroidism and persistent deterioration of quality of life despite biochemically adequate treatment with levothyroxine, showed a striking improvement in quality of life, as assessed by the ThyPRO-39, after switching from levothyroxine to a combination of levothyroxine and liothyronine [32]. Although the authors suggested a possible direct benefit of combination therapy, they did not draw attention to the fact that TSH levels had dropped significantly 3 months after change of treatment, which might suggest that patients improved simply because of the greater potency of the combination therapy, reflected by decreased TSH levels. The benefits seen with lower TSH values in certain hypothyroid patients could be related to the fact that TSH levels are genetically determined [33] and oscillate around the endogenous set point of each individual. In fact, the intraindividual variation of TSH is less than its interindividual variation [34]. Therefore, the whole normal TSH range applicable to the general population could not be suitable for some particular subjects with a lower TSH set point. However, the normal TSH values of each individual before diagnosis of hypothyroidism are often not known, and, in any case, it is not common practice to take them into account when setting the therapeutic goal after diagnosis.

This study has obvious limitations. First, its sample size was small, and its results are based on a single TSH determination for each patient. In addition, the levels of circulating thyroid hormones (T4 or T3), which maybe could offer a better correlation with quality of life than TSH, as well as other potential confounding factors, such as antithyroid antibodies, were not measured.

In conclusion, this study shows that, even within the normal reference range, TSH levels correlate with quality of life among patients with primary hypothyroidism treated

with levothyroxine. The assessment of selected patient-reported outcomes could be used to make fine adjustments to the dose of levothyroxine replacement therapy.

Author contributions The investigation was planned by M.B., although all authors contributed to the conception and study design. Material preparation and data collection were performed by M.M.-D., M.P.A.-R., C.A.R.-P., Y.L.-P., D.M.-A., and A.M.G.-L. Statitiscal analyses were performed by P.S. The first draft of the manuscript was written by M.B. and M.M.-D. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Complejo Hospitalario Universitario Insular Materno-Infantil.

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