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Is Thyroid Autoimmunity per se a Determinant of Quality of Life in Patients with Autoimmune Hypothyroidism?

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Key Words
Autoimmune hypothyroidism · Quality of life · Clinical variables · Autoimmunity

Abstract
Purpose: To evaluate the relationship between thyroid variables and health-related quality of life (QoL) in patients with autoimmune hypothyroidism, using the thyroid-specific QoL questionnaire ThyPRO. ***Methods:*** In a cross-sectional study, responses to the ThyPRO from 199 outpatients with autoimmune hypothyroidism were analyzed in relation to thyroid volume, thyroid function and markers of thyroid autoimmunity. Based on a classical QoL framework, we hypothesized that physiological dysfunction caused specific physical and psychological symptoms, which affected functioning and well-being, and consequently participation in life and QoL. These hypotheses were tested through multiple regression and multivariate path analysis models. ***Results:*** None of the thyroid function tests were associated with QoL scores. However, in the pairwise regression, the thyroid peroxidase antibody (TPOAb) level was associated with several QoL outcomes: Goitre Symptoms ($p = 0.024$), Depressivity ($p = 0.004$), Anxiety ($p = 0.004$), Emotional Susceptibility ($p = 0.005$) and Impaired Social Life ($p = 0.047$). In the multivariate model, the TPOAb level was related to Goitre Symptoms ($r = 0.17$, $p = 0.019$), Depressivity ($r = 0.24$, $p = 0.001$), and Anxiety ($r = 0.23$, $p = 0.002$), but no longer to Emotional Susceptibility or Impaired Social Life, indicating that the effect on these were mediated through an effect on the symptom scales (i.e. Goitre Symptoms, Depressivity and Anxiety). ***Conclusion:*** Health-related QoL, evaluated with state-of-the-art QoL methodology, was related to TPOAb level but not to thyroid function. This raises the hypothesis that autoimmunity, independent of thyroid function, impacts on QoL in patients with autoimmune hypothyroidism, especially in terms of psychological symptoms. Longitudinal studies, in initially untreated patients, are needed to test this hypothesis.

Introduction

Autoimmune hypothyroidism is characterized by lymphocytic infiltration of the thyroid gland and most commonly various degrees of hypofunctioning of the gland, in the presence of thyroid autoantibodies against thyroid peroxidase (TPOAb) and/or thyroglobulin

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Table 1. Clinical and sociodemographic characteristics of the 199 patients with autoimmune hypothyroidism

Women/men, n	184 (92%)/15
Age, years	44 (19–88)
Months since diagnosis[1]	21 (–0.7 to 307)
Diagnosed with mild hypothyroidism[2]	69 (36)[3]
Currently treated with L-thyroxine	152 (77%)
Thyroid volume, ml	9 (0–55)
TSH, mIU/l	3.1 (<0.01–54.8)
FreeT_4, pmol/l	16 (0.2–163)
Free T_3, pmol/l	4.8 (1.6–7.6)
TPOAb, U/l	4,266 (0–21,952)
TSHRAb, U/l	0 (0–7)

Data presented as numbers and percentages and medians and ranges. TSHRAb = TSH receptor antibody levels.

[1] Negative duration due to a patient completing the questionnaire before a final diagnosis was reached.

[2] Serum TSH above reference range and peripheral thyroid hormones within reference range (also termed subclinical hypothyroidism).

[3] Data for determination of mild or overt hypothyroidism at time of diagnosis (i.e. up to several years prior to questionnaire completion) were unavailable for 8 patients.

(TGAb). The condition is associated with a wide range of unspecific symptoms.

In recent years, a change of paradigm has occurred in the treatment of many chronic diseases. Restoring physiological imbalances is no longer seen as an aim in itself, but rather as a means towards prolonging life, relieving symptoms and improving function. Thus, evaluation of such outcomes is central in chronic-disease treatment evaluation [1]. While the paradigm shift has come late to thyroid diseases, this area represents obvious beneficial applications. Thyroid diseases such as autoimmune hypothyroidism are common, chronic, and affect the patients' function and quality of life (QoL) [2, 3]. Despite this high prevalence, few systematic studies have evaluated the impact of autoimmune hypothyroidism on QoL and until recently, no validated measure of QoL for thyroid patients was available [4].

QoL is a complex and multidimensional construct. Studies of QoL in patient populations should acknowledge this, by incorporating analyses of QoL into a theoretical and statistical model reflecting this complexity [5]. In order for such a model to reflect the disease in focus, the theoretical model should incorporate clinical variables and the hypothesized relationship between these and the QoL framework [5, 6]. The advent of a comprehensive, thoroughly validated thyroid-specific patient-reported outcome measuring health-related QoL for patients with thyroid diseases, i.e. ThyPRO [7–10], calls for studies evaluating these relationships between clinical variables and QoL.

The purpose of the present study was therefore to evaluate the relationship between clinical measures of disease activity and health-related QoL in patients with autoimmune hypothyroidism using the thyroid-specific QoL questionnaire ThyPRO and subjecting data to multivariate analysis within a theoretical QoL framework.

Methods

Patients and Procedures

During February to November 2007, 199 patients with autoimmune hypothyroidism (defined as any degree of serum thyroid-stimulating hormone (TSH) above the reference range at two consecutive measurements, with or without associated thyroid hormone levels below the reference range, and TPOAb level >60 IU/l), attending the endocrinological outpatient clinics at Copenhagen University Hospital Rigshospitalet and Odense University Hospital were recruited (table 1). None of the patients had eye involvement. Recruitment has previously been described in detail [9] and the overall response rate was 69%. Questionnaires were completed and blood samples were drawn a few days prior to the scheduled visit to the clinic. A physical examination, including thyroid ultrasound, was performed and written, signed informed consent obtained.

Sociodemographic data and information about comorbidity and nonthyroid medication were self-reported. Data regarding clinical biochemical measurements and thyroid imaging, exact diagnosis, previous and current treatment and time of diagnosis were obtained by chart review. Biochemical thyroid tests, using in-house routine assays, were TSH, total thyroxine (T_4), total triiodothyronine (T_3), non-protein-bound thyroxine (fT_4), non-protein-bound triiodothyronine (fT_3) and TPOAb. Thyroid volume was determined by ultrasound using the ellipsoid method [11]. The project was approved by the local ethical committee (KF01 2006-1579) and the Danish data protection agency and registered at ClinicalTrials.gov (NCT00150033).

Patient-Reported Outcome, ThyPRO

The ThyPRO is an 84-item thyroid-specific patient-reported outcome measuring QoL with 13 scales covering physical and mental symptoms, functioning and well-being as well as impaired participation in important life activities. The content was derived by literature review and in-depth interviews with experts and patients [7]; the instrument has been validated for thyroid patients [8–10]. Each item is rated by the patient on a five-point Likert scale, and the 13 scales are derived by averaging and linearly transforming these item scores into their respective 0–100 scale score. Figure 1 is a representation of these scales, organized in a conceptual model linking health-related QoL and clinical variables [6, 12] for patients with any benign thyroid disease (see below).

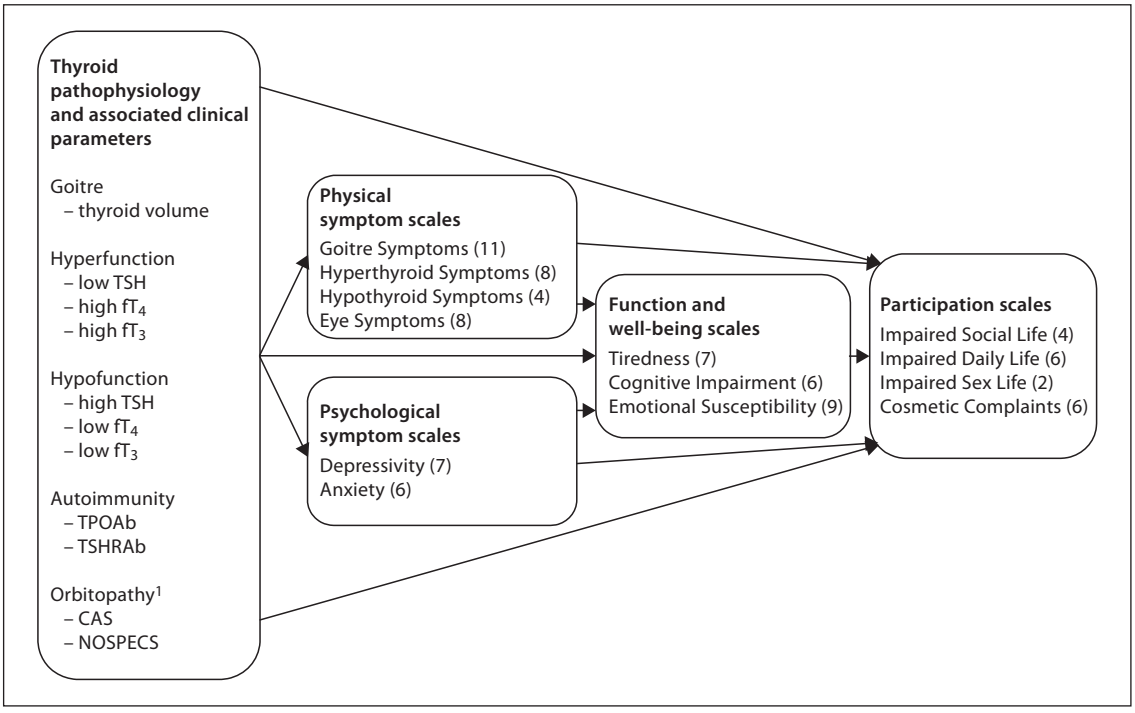

Fig. 1. Conceptual model linking the ThyPRO QoL scales with the relevant clinical variables. To the left are pathophysiological mechanisms involved in thyroid diseases and the clinical variables representing these mechanisms. The 13 scales, with the number of items in each scale in parentheses, are organized in their respective overall categories. TSHRAb = TSH receptor antibody. [1] Not relevant in this sample, but included in the figure for completeness of the model.

Theoretical QoL Model

The theoretical QoL model, incorporating the hypothesized relationships, is presented in figure 1: thyroid volume is related to goitre symptoms; low serum TSH, high serum fT_4, and high serum fT_3 cause hyperthyroid symptoms; high serum TSH, low serum fT_4 and low serum fT_3 cause hypothyroid symptoms; Clinical Activity Score (CAS) [13] and NOSPECS, an orbitopathy grading system [14], are associated with eye symptoms (not relevant in this sample), and TPOAb and TSHRAb could be associated with all the symptom scales. Further, physical and psychological symptoms are associated with reduced function and well-being and these reductions again affect social life, daily life, sex life and body image.

The segregation of the thyroid function into higher versus lower function is due to the fact that a linear, or just incremental, relationship between thyroid function and QoL cannot be expected. This relationship must be U-shaped with e.g. *decreasing* serum TSH *below* the reference range leading to decreasing QoL due to hyperthyroidism whereas *increasing* TSH *above* the reference range also leads to *decreasing*, and not increasing, QoL. Therefore, when analyzing thyroid hyperfunction within the model, serum TSH values above the general population median, and serum T_4 and serum T_3 values below the median were set to missing. Similarly, when analyzing hypofunction, serum TSH values below the median in the general population and serum T_4 and serum T_3 above the median were set to missing.

Statistical Analyses

Initially, pairwise relationships between all variables in the theoretical model were analyzed univariately, controlling for age, gender and educational level, using SAS 9.1.3 PROC GLM [15].

Subsequently, statistically significant associations ($p < 0.05$) were joined in one overall path model, using Mplus [16] with maximum likelihood estimation. Model results were checked for colinearity between hormone measurements and nonnormal distribution of clinical variables, particularly serum TSH, which was also entered as squared and cubed values.

To test the stability of the results, several post hoc analyses were performed. In the univariate pairwise analyses of the relationship between QoL scales and thyroid function, the latter was also operationalized as (a) current thyroid function, i.e. euthyroidism (n = 92, 46%), mild hypothyroidism (n = 77, 39%), overt hypothyroidism (n = 3, 2%), mild hyperthyroidism (i.e. overtreated) (n = 14, 7%) and overt hyperthyroidism (n = 8, 4%); (b) current euthyroidism (euthyroidism vs. any dysfunction) and (c) degree of dysfunction at the time of diagnosis (mild vs. overt hypothyroidism). The multivariate analysis concerning relationships with thyroid autoimmunity was repeated, controlling for (a) age, (b) duration of disease, (c) whether or not on L-thyroxine replacement therapy, (d) dosage and duration of L-thyroxine therapy and (e) current thyroid function (euthyroidism, mild/overt hypothyroidism and hyperthyroidism) by adding these variables as covariates to the regression equations.

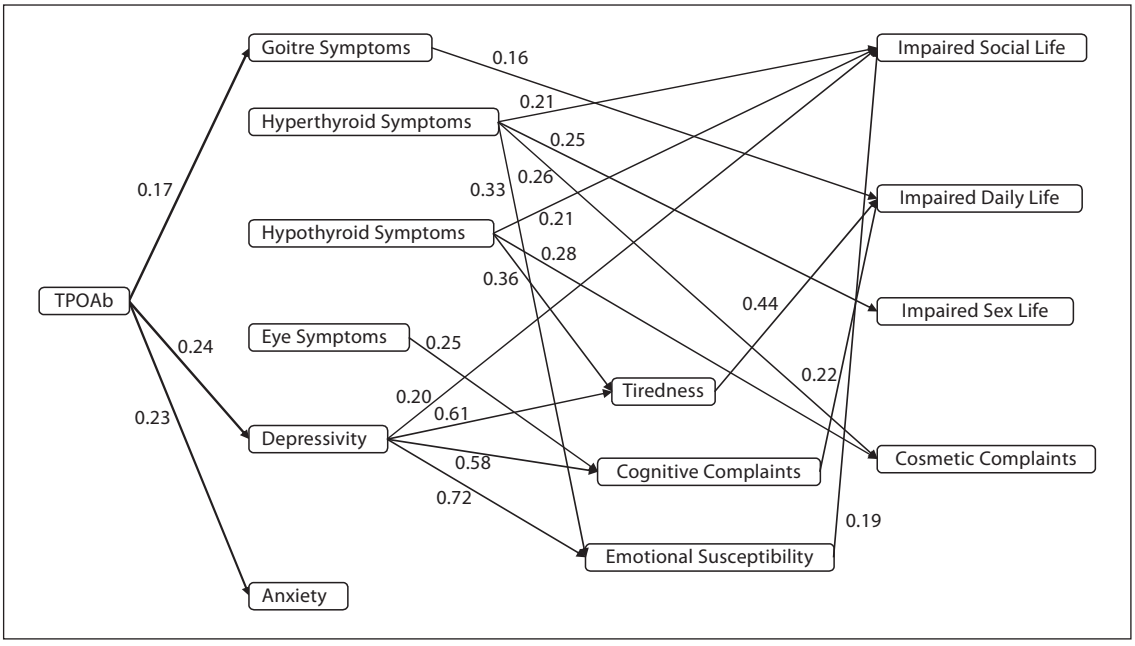

Fig. 2 Results of the multivariate path analysis. ThyPRO scales are ordered in accordance with the theoretical QoL model. Standardized regression coefficients estimating the strength of the association are presented along each association arrow. Standardization implies that e.g. an increase of 1 SD in TPOAb leads to a 0.24-SD increase in Depressivity.

Results

Univariate Associations

In the univariate, controlled comparisons, clinical variables measuring goitre (i.e. thyroid volume), thyroid dysfunction (i.e. TSH, T_4 and T_3) and eye involvement (i.e. CAS and NOSPECS) were not related to QoL scores. TPOAb levels were statistically significantly associated with several QoL dimensions: Goitre Symptoms ($p = 0.024$), Depressivity ($p = 0.004$), Anxiety ($p = 0.004$), Emotional Susceptibility ($p = 0.005$) and Impaired Social Life ($p = 0.047$).

In the controlling post hoc analyses, none of the alternative operationalizations of thyroid function was associated with QoL scores.

Multivariate Path Model

In the path analysis multivariate model, TPOAb was related to the symptom scales: Goitre ($p = 0.019$), Depressivity ($p = 0.001$) and Anxiety ($p = 0.002$) but no longer to Emotional Susceptibility or Impaired Social Life (fig. 2). Post hoc analyses controlled for age, duration of disease, whether the patient was being treated with L-thyroxine and the dosage and duration of this treatment, current thyroid function status as well as transforming relevant clinical variables (see above) did not significantly change the results (data not shown).

Discussion

The purpose of the present study was to evaluate the relationship between clinical measures of disease activity and health-related QoL in patients with autoimmune hypothyroidism.

In univariate comparisons between the relevant clinical variables and the ThyPRO QoL scales, no relationship between measures of thyroid dysfunction was found. In contrast, TPOAb levels were related to several ThyPRO scales, both symptoms scales and scales measuring well-being and function as well as participation. The findings were repeated when the data were subjected to multivariate analysis within a theoretical QoL framework, with the exception that now TPOAb levels were only related to the symptom scales. The relationship between TPOAb and the function and well-being scale, Emotional Susceptibility, and the participation scale, Impaired Social Life, thus seem to be through an association with Depressivity.

It is surprising that we did not find any relationship between thyroid function and QoL. This finding was consistent, regardless of the way thyroid (dys-)function was operationalized, as exemplified in our post hoc analyses. We therefore also conducted post hoc repetitions of the multivariate analyses, where various operationalizations of thyroid (dys-)function were entered as covariates to all paths involving TPOAb. We also controlled the analyses for age and various other clinically relevant variables. Still, only TPOAb and not thyroid function was related to QoL. However, this is probably due to the fact that the vast majority of patients were only marginally dysthyroid at the time of participation, as a consequence of the sampling procedure spanning all disease stages, including well-treated (and even over-treated) patients. Almost half of the patients were euthyroid at the time of the study and only 2% were overtly hypothyroid. This may have been different if more patients with current overt hypothyroidism had been included. Indeed, Canaris et al. [17] and others [18, 19] have demonstrated a relationship between hypothyroid symptoms and thyroid function, when investigating patients with overt hypothyroidism and euthyroid controls. Another recent study among 597 patients receiving L-thyroxine (73% of whom had autoimmune hypothyroidism) found an association between psychological well-being and fT4 and serum TSH, but not fT3 or TPOAb positivity [20]. However, TPOAb were analyzed as a dichotomized, and not as a continuous variable as in our study, which could explain this difference. In accordance with our findings, Ott et al. [21] demonstrated a correlation between the level of TPOAb, but not thyroid function tests, and scores on an unvalidated symptom questionnaire, in a study of patients undergoing thyroidectomy for benign goitre. Another field of research has focused on the role of thyroid autoimmunity in musculoskeletal complaints, particularly fibromyalgia [22, 23]. For example, Bazzichi et al. [22] found comorbidity with and higher levels of symptoms of fibromyalgia in patients with Hashimoto's thyroiditis and subclinical hypothyroidism, in contrast to patients with nonautoimmune subclinical hypothyroidism. Additionally, in a population-based study, a higher prevalence of TPOAb positivity was found in respondents with musculoskeletal complaints, compared to those without [24]. An interesting study supposed a possible mechanism of action: Marquez et al. [25] found microvascular alterations similar to those observed in other autoimmune diseases in skeletal muscle from patients with autoimmune thyroiditis, independent of thyroid function. These capillary alterations included changes in basement membranes and endothelial thickening, but also signs of capillary degeneration. It may be hypothesized that such microvascular alterations could also be present in other biological structures, including the central nervous system, and thus explain the associations between autoimmunity and neck-related symptoms as well as mental health observed in the present study.

Several studies have indicated a link between the thyroid gland and mental diseases [26]. As for autoimmune thyroid diseases, Pop et al. [27] found a three times higher risk of current depression (according to the Edinburg Depression Scale) in individuals with positive TPOAb in a large population-based study and the presence of TPOAb during pregnancy has been identified as a risk factor for postpartum depression [28].

A direct relation between thyroid autoimmunity and affected QoL has also been hypothesized to be at play in the rare and controversial diagnosis of Hashimoto's encephalopathy, where a variety of neurological symptoms have been linked to the presence of TPOAb [29].

As its main strength, our study is the first to apply a thoroughly validated, thyroid-specific QoL instrument. Investigation of the associations between clinical and QoL variables in an explicit theoretical framework, in clinically well-characterized individuals, adds further validity and novelty to our findings.

The main limitation of our study is its cross-sectional design, the relatively limited range in thyroid dysfunction, and the few severely hypothyroid individuals. Future hypothesis-testing studies should adopt a longitudinal design, compare changes in all available thyroid autoantibodies, or even better various epitopes of these antibodies [30–34], and in thyroid function, with changes in QoL. Also, the relationship between such indicators of thyroid autoimmunity and QoL could be evaluated in a sample of patients with autoimmune thyroiditis and normal thyroid function. Applying diagnostic imaging, such as e.g. MR spectroscopy [35], may offer further insight into the possible CNS effect and thereby the link with affected QoL measures.

Future interventional research may target the autoimmune component of the disease more directly. For example, by investigating the effect on QoL of selenium supplementation [36], which appears to lower TPOAb levels, glucocorticoid therapy or novel biological therapies, such as rituximab [37]. Future studies focusing on QoL methodology could further develop and investigate the theoretical framework and its relationship with clinical variables. Accepting that patients with chronic autoimmune thyroiditis, with or without thyroid dysfunc-

tion, have increased morbidity and decreased QoL, but seemingly no increase in mortality [38], remains a conundrum and needs further study.

In conclusion, TPOAb level, but not thyroid function, was related to thyroid-specific QoL. This raises the hypothesis that thyroid autoimmunity may play a role, independent of thyroid dysfunction, in the QoL impairment associated with autoimmune hypothyroidism. Future studies should focus on individuals with a broader range of TPOAb as well as thyroid dysfunction in longitudinal and interventional studies, employing a validated questionnaire such as the ThyPRO for QoL determination.

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Disclosure Statement

The authors have no conflicts of interest to declare and have nothing to disclose.

References

1 US Food and Drug administration: Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

2 Bianchi GP, Zaccheroni V, Solaroli E, et al: Health-related quality of life in patients with thyroid disorders. Qual Life Res 2004;13:45–54.

3 Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM: Psychological well-being in patients on 'adequate' doses of L-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf) 2002;57:577–585.

4 Watt T, Groenvold M, Rasmussen AK, et al: Quality of life in patients with benign thyroid disorders. A review. Eur J Endocrinol 2006;154:501–510.

5 Hays RD, Revicki D, Coyne KS: Application of structural equation modeling to health outcomes research. Eval Health Prof 2005; 28:295–309.

6 Wilson IB, Cleary PD: Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995;273:59–65.

7 Watt T, Hegedüs L, Rasmussen AK, et al: Which domains of thyroid-related quality of life are most relevant? Patients and clinicians provide complementary perspectives. Thyroid 2007;17:647–654.

8 Watt T, Rasmussen AK, Groenvold M, et al: Improving a newly developed patient-reported outcome for thyroid patients, using cognitive interviewing. Qual Life Res 2008; 17:1009–1017.

9 Watt T, Bjorner JB, Groenvold M, et al: Establishing construct validity for the thyroid-specific patient reported outcome measure (ThyPRO): an initial examination. Qual Life Res 2009;18:483–496.

10 Watt T, Hegedüs L, Groenvold M, et al: Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. Eur J Endocrinol 2010;162:161–167.

11 Hegedüs L: Thyroid ultrasound. Endocrinol Metab Clin North Am 2001;30:339–360.

12 Ware JE Jr: Conceptualization and measurement of health-related quality of life: comments on an evolving field. Arch Phys Med Rehabil 2003;84(suppl 2):S43–S51.

13 Mourits MP, Prummel MF, Wiersinga WM, Koornneef L: Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf) 1997;47:9–14.

14 Werner SC: Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of the American Thyroid Association. J Clin Endocrinol Metab 1977;44:203–204.

15 SAS Institute Inc SAS/STAT 9.1 User's Guide, ed 4. Cary, SAS Institue Inc, 2004.

16 Muthén B, Muthén L: Mplus User Guide, ed 6. Los Angeles, Muthén & Muthén, 2010.

17 Canaris GJ, Steiner JF, Ridgway EC: Do traditional symptoms of hypothyroidism correlate with biochemical disease? J Gen Int Med 1997;12:544–550.

18 Billewicz WZ, Chapman RS, Crooks J, et al: Statistical methods applied to the diagnosis of hypothyroidism. QJM 1969;38:255–266.

19 Barker DJ, Bishop JM: Computer-based screening system for patients at risk of hypothyroidism. Lancet 1969;ii:835–838.

20 Saravanan P, Visser TJ, Dayan CM: Psychological well-being correlates with free thyroxine but not free 3,5,3′-triiodothyronine levels in patients on thyroid hormone replacement. J Clin Endocrinol Metab 2006;91: 3389–3393.

21 Ott J, Promberger R, Kober F, et al: Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: a prospective case-control study in women undergoing thyroidectomy for benign goiter. Thyroid 2011;21:161–167.

22 Bazzichi L, Rossi A, Zirafa C, et al: Thyroid autoimmunity may represent a predisposition for the development of fibromyalgia? Rheumatol Int 2012;32:335–341.

23 Dardano A, Bazzzichi L, Bombardieri S, Monzani F: Symptoms in euthyroid Hashimoto's thyroiditis: is there a role for autoimmunity itself? Thyroid 2012;22:334–335.

24 Aarflot T, Bruusgaard D: Association between chronic widespread musculoskeletal complaints and thyroid autoimmunity. Results from a community survey. Scand J Prim Health Care 1996;14:111–115.

25 Marquez A, Finol HJ, De Blanco MC, Adjounian H, Pulido-Mendez M: Skeletal muscle microvascular alterations in euthyroid and hypothyroid patients with autoimmune thyroid disease. J Submicrosc Cytol Pathol 2001; 33:425–432.

26 Bauer M, Goetz T, Glenn T, Whybrow PC: The thyroid-brain interaction in thyroid disorders and mood disorders. J Neuroendocrinol 2008;20:1101–1114.

27 Pop VJ, Maartens LH, Leusink G, et al: Are autoimmune thyroid dysfunction and depression related? J Clin Endocrinol Metab 1998;83:3194–3197.

28 Kuijpens JL, Vader HL, Drexhage HA, Wiersinga WM, van Son MJ, Pop VJ: Thyroid peroxidase antibodies during gestation are a marker for subsequent depression postpartum. Eur J Endocrinol 2001;145:579–584.
29 Schiess N, Pardo CA: Hashimoto's encephalopathy. Ann NY Acad Sci 2008;1142:254–265.
30 Brix TH, Hegedüs L, Gardas A, Banga JP, Nielsen CH: Monozygotic twin pairs discordant for Hashimoto's thyroiditis share a high proportion of thyroid peroxidase autoantibodies to the immunodominant region A. Further evidence for genetic transmission of epitopic 'fingerprints'. Autoimmunity 2011; 44:188–194.
31 Latrofa F, Ricci D, Vitti P, et al: Characterization of thyroglobulin epitopes in Sardinian adults and juveniles with Hashimoto's thyroiditis: evidence against a major effect of age and genetic background on B-cell epitopes. Clin Endocrinol (Oxf) 2010;73:110–113.
32 McLachlan SM, Feldt-Rasmussen U, Young ET, et al: IgG subclass distribution of thyroid autoantibodies: a 'fingerprint' of an individual's response to thyroglobulin and thyroid microsomal antigen. Clin Endocrinol (Oxf) 1987;26:335–346.
33 Ruf J, Feldt-Rasmussen U, Hegedus L, Ferrand M, Carayon P: Bispecific thyroglobulin and thyroperoxidase autoantibodies in patients with various thyroid and autoimmune diseases. J Clin Endocrinol Metab 1994;79: 1404–1409.
34 Rasmussen AK, Feldt-Rasmussen U, Brandt M, Hartoft-Nielsen ML, Carayon P, Buschard K: Thyrotropin stimulates specifically the expression of the autoantibody binding domains of the thyroperoxidase molecule. Autoimmunity 1999;29:323–331.
35 Elberling TV, Danielsen ER, Rasmussen AK, Feldt-Rasmussen U, Waldemar G, Thomsen C: Reduced myo-inositol and total choline measured with cerebral MRS in acute thyrotoxic Graves' disease. Neurology 2003;60: 142–145.
36 Toulis KA, Anastasilakis AD, Tzellos TG, Goulis DG, Kouvelas D: Selenium supplementation in the treatment of Hashimoto's thyroiditis: a systematic review and a meta-analysis. Thyroid 2010;20:1163–1173.
37 Hegedüs L, Smith TJ, Douglas RS, Nielsen CH: Targeted biological therapies for Graves' disease and thyroid-associated ophthalmopathy. Focus on B-cell depletion with Rituximab. Clin Endocrinol (Oxf) 2011;74:1–8.
38 Thvilum M, Brandt F, Brix TH, Hegedüs L: A review of the evidence for and against increased mortality in hypothyroidism. Nat Rev Endocrinol 2012;8:417–424.