CLINICAL STUDY

Fatigue and fatigue-related symptoms in patients treated for different causes of hypothyroidism

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Abstract

Objective: Research on determinants of well-being in patients on thyroid hormone replacement therapy is warranted, as persistent fatigue-related complaints are common in this population. In this study, we evaluated the impact of different states of hypothyroidism on fatigue and fatigue-related symptoms. Furthermore, the relationship between fatigue and the TSH receptor (TSHR)-Asp727Glu polymorphism, a common genetic variant of the TSHR, was analyzed.

Design: A cross-sectional study was performed in 278 patients (140 patients treated for differentiated thyroid carcinoma (DTC) and 138 with autoimmune hypothyroidism (AIH)) genotyped for the TSHR-Asp727Glu polymorphism.

Methods: The multidimensional fatigue inventory (MFI-20) was used to assess fatigue, with higher MFI-20 scores indicating more fatigue-related complaints. MFI-20 scores were related to disease status and Asp727Glu polymorphism status.

Results: AIH patients scored significantly higher than DTC patients on all five MFI-20 subscales ($P < 0.001$), independent of clinical and thyroid hormone parameters. The frequency of the TSHR-Glu727 allele was 7.2%. Heterozygous DTC patients had more favorable MFI-20 scores than wild-type DTC patients on four of five subscales. The modest effect of the TSHR-Asp727Glu polymorphism on fatigue was found in DTC patients only.

Conclusions: AIH patients had significantly higher levels of fatigue compared with DTC patients, which could not be attributed to clinical or thyroid hormone parameters. The modest effect of the TSHR-Asp727Glu polymorphism on fatigue in DTC patients should be confirmed in other cohorts.

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Introduction

Awareness of psychological and physical dysfunction in patients on thyroid hormone therapy is important. Many hypothyroid patients experience persistent fatigue and fatigue-related symptoms, as well as poor performance on various domains of neurocognitive functioning, despite apparently adequate replacement therapy (1, 2). The origin of hypothyroidism, and also genetic variation in thyroid hormone pathway genes and variation in local thyroid hormone profile, may be of importance to explain these findings.

TSH plays a central role in regulation of thyroid function and exerts its effects through binding to the TSH receptor (TSHR). Although primarily expressed on thyroid follicular cells, evidence suggests TSHR expression in the anterior pituitary, adipose tissue, retro-orbital tissue, osteoblasts, the immune system,

and cardiac muscle (3, 4, 5, 6, 7, 8, 9, 10). In addition, expression of TSHR mRNA has been reported in several regions of the mammalian, including human, brain (11, 12, 13, 14, 15). These findings indicate that the role of TSH is not merely restricted to hypothalamus–pituitary–thyroid axis regulation (7, 8, 15, 16, 17).

The TSHR-Asp727Glu polymorphism is a common genetic variant, leading to an amino acid substitution in the intracellular domain of the TSHR (18). The TSHR-Glu727 variant has been proposed to have higher activity than the wild-type variant because less TSH is required to maintain normal serum free thyroxine (FT₄) levels (19, 20, 21), indicating higher sensitivity of the receptor. Previous reports have assessed the effect of the TSHR-Asp727Glu polymorphism on various clinical outcomes, including bone metabolism, glucose metabolism, and preeclampsia (21, 22, 23, 24). Furthermore, a TSHR-mediated mechanism was proposed to be

involved in stimulation of type 2 iodothyronine deiodinase (D2) expression in various tissues (7, 8, 15). This process may be an important determinant of the local concentration of the biologically active thyroid hormone triiodothyronine (T_3) as D2 catalyzes the conversion of T_4 to T_3 (25). It could be hypothesized that in the CNS of individuals with the TSHR-Glu727 variant, a more sensitive TSHR increases the ability of neurons to adjust intracellular thyroid hormone levels, thereby affecting neuropsychological functioning.

The aim of this study was to assess the impact of the cause of hypothyroidism on fatigue and fatigue-related symptoms in two independent cohorts of patients treated for hypothyroidism of different origin, i.e. thyroidectomized patients treated for differentiated thyroid carcinoma (DTC) and patients with autoimmune hypothyroidism (AIH). Secondly, it was studied whether an effect of the TSHR-Asp727Glu polymorphism on fatigue and fatigue-related symptoms could be found.

Materials and methods

Study design and study population

We performed a cross-sectional study in patients on thyroid hormone replacement therapy for hypothyroidism for either DTC or AIH (Fig. 1). The present analyses were based on previously included and phenotyped cohorts (22, 26), which therefore determined the sample size (27).

The study comprised 292 patients: 149 patients treated for DTC from Leiden University Medical Centre and 143 patients with AIH from the Academic Medical Centre of the University of Amsterdam. Written informed consent was provided by all patients and the institutional review boards approved the study. Fourteen patients were excluded: genotyping failed

in seven patients and seven additional patients did not return the fatigue questionnaire. A total of 278 patients were included to assess the relationship between fatigue questionnaire scores and genotype status (Fig. 1).

All DTC patients had been treated by total thyroidectomy followed by routine postoperative radioiodine ablation therapy and were without signs of persistent or recurrent disease at time of evaluation (22). The diagnosis of AIH was based on biochemically proven hypothyroidism, measurement of TPO antibodies, and exclusion of secondary causes (28). Patients in both cohorts were on thyroid hormone replacement therapy. In DTC patients, thyroid hormone replacement therapy was aimed at TSH suppression to prevent disease recurrence, while for AIH the target for T_4 replacement was a TSH in the reference range (RR).

Fatigue questionnaire

The multidimensional fatigue inventory (MFI-20) was used to assess fatigue. The MFI-20 is a 20-item self-report questionnaire covering five dimensions of fatigue, which are measured on a five-point scale. The five dimensions are general fatigue, physical fatigue, reduction in activities, reduction in motivation, and mental fatigue. 'General fatigue' includes general statements concerning a person's functioning such as 'I feel rested'. 'Physical fatigue' refers to the physical sensation of feeling tired. Somatic symptoms, such as light-headedness or sore muscles, are not included in the scale in order to exclude potential contamination with the symptoms of somatic illness, independent of fatigue. Reduction in activities and lack of motivation to start any activity are covered by the scales 'Reduced activities' and 'Reduced motivation' respectively. Finally, cognitive symptoms such as having difficulties concentrating are included in the scale for 'Mental fatigue'. Scores vary from 0 to 20; higher scores indicate greater fatigue (29, 30).

Genotyping

For genotyping of the TSHR-Asp727Glu polymorphism, DNA was isolated from peripheral leucocytes by the salting out procedure (31). Genotyping was performed using 5 ng genomic DNA by a 50-fluorogenic TaqMan assay and reactions were performed in 384-wells format on ABI9700 2x384-well PCR machines with end point reading on the ABI 7900HT TaqMan machine (Applied Biosystems, Nieuwerkerk aan den IJssel, The Netherlands). Primer and probe sequences were optimized using the single nucleotide polymorphism assay-by-design service of Applied Biosystems. Genotypes were classified as wild type (Asp/Asp), heterozygous (Asp/Glu), or homozygous (Glu/Glu) for the TSHR-Asp727Glu polymorphism.

Figure 1 Flow chart of included patients.

Laboratory examination

Morning blood samples were drawn before thyroid hormone intake and stored at -80°C . In the DTC population, serum FT₄ (RR 10–24 pmol/l) and TSH levels (RR 0.3–4.8 mU/l) were measured by electrochemiluminescence immunoassay using a Modular Analytics E-170 system (intra-assay CV of 1.6–2.2 and 1.3–5.0% respectively (Roche)). Serum T₃ (RR 1.27–2.39 nmol/l) and T₄ (RR 70–138 nmol/l) were analyzed by RIA. The maximum intra-assay CV were 5.8 (T₃) and 7.7% (T₄). In the AIH patients, FT₄ (RR 10–23 pmol/l) was analyzed by fluoroimmunoassay (Delfia P1232 Fluorometer, Perkin Elmer, Waltham, MA, USA). The maximal intra- and interassay variations were 5.1 and 6.8% respectively. Serum TSH (RR 0.4–4.0 mU/l) was analyzed by solid-phase two-site fluoro-immunometric assay (IFMA, Perkin Elmer). The maximal intra- and interassay variations were <5 and 7.7% respectively. Serum T₃ (RR 1.3–2.7 nmol/l) and T₄ levels (RR 70–150 nmol/l) were measured by RIA (32). The maximal intra- and interassay variations were 6.3 and 7.8% (T₃) and 5.4 and 8.7% (T₄) respectively.

Statistical analysis

Different FT₄, TSH, T₃, and T₄ assays were used in the two cohorts. In order to obtain comparable RRs, standardized z-scores were calculated for thyroid parameters in the DTC cohort. In a second step, these z-scores were applied to the RRs of the thyroid parameters in the AIH cohort.

Data are presented as mean $\pm$ s.d., median (range), or proportions as appropriate. Baseline characteristics, thyroid parameters, and MFI-20 scores were categorized by disease (DTC vs AIH) as well as genotype status.

Potential deviations from Hardy–Weinberg equilibrium were assessed by a χ^2 test. Differences in clinical parameters and thyroid parameters were analyzed by *t*-tests and χ^2 tests, as appropriate. Mean differences (MD) with accompanying 95% confidence intervals (95% CI) were presented for continuous variables. TSH levels were log-transformed to normalize distribution.

The association between MFI-20 scores and disease or genotype status was analyzed by linear regression. All analyses were adjusted for age and gender, and subsequently, BMI, TSH, T₃, T₄, and FT₄ were added to the model to account for a potential confounding effect of these factors.

To disentangle effects of diagnosis (DTC vs AIH) on fatigue from effects of the polymorphism, an interaction analysis was performed. Because of the linearity of the regression model used, a significant interaction was interpreted as departure from additivity. Interaction was tested with a Wald test. Statistical analyses were carried out using SPSS 17.0 for windows (SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics and MFI-20 scores

A total of 278 patients were included in the study: 140 treated for DTC and 138 treated for AIH (Table 1). Mean age of all patients was 48.8 years; 233 (84%) were female. Median duration of cure after treatment for DTC was 6.4 years (range 0.5–41.8 years). DTC patients were on thyroid hormone replacement therapy for longer than AIH patients (median: 9.2 vs 5.5 years).

As expected, DTC patients had lower TSH levels than AIH patients (median: 0.07 vs 1.20 mU/l) and higher FT₄ levels (21.5 vs 14.7 pmol/l), reflecting a

Table 1 Study characteristics by cause of hypothyroidism. Data are expressed as mean $\pm$ s.d., median (range), or percentage as appropriate.

	Total population (n=278)	DTC (n=140)	AIH (n=138)	Mean differences (95% CI)	P value ^a
General characteristics					
Age (years)	48.8 $\pm$ 11.6	49.3 $\pm$ 13.3	48.3 $\pm$ 9.8	−1.0 (−3.7; 1.7)	0.485
Sex (female, %)	83.8	81.4	86.2	ND	0.277
BMI (kg/m ²)	27.3 $\pm$ 5.7	25.7 $\pm$ 4.6	28.7 $\pm$ 6.3	3.0 (1.7; 4.3)	<0.001
Thyroid function parameters					
TSH (mU/l)	0.49 (0.01; 6.50)	0.07 (0.01; 5.35)	1.20 (0.04; 6.50)	2.31 (2.00; 2.63)	<0.001 ^b
T ₄ (nmol/l)	136.3 $\pm$ 38.6	150.6 $\pm$ 45.4	123.6 $\pm$ 25.4	−26.6 (−35.5; −17.8)	<0.001
T ₃ (nmol/l)	1.64 $\pm$ 0.38	1.56 $\pm$ 0.42	1.72 $\pm$ 0.32	0.16 (0.07; 0.25)	0.001
FT ₄ (pmol/l)	17.9 $\pm$ 4.9	21.5 $\pm$ 4.1	14.7 $\pm$ 2.8	−6.8 (−7.6; −5.9)	<0.001
T ₄ dose (μ g/kg)	1.88 $\pm$ 0.88	2.13 $\pm$ 1.02	1.59 $\pm$ 0.65	−0.57 (−0.77; −0.37)	<0.001
MFI-20 scores					
General fatigue	13.1 $\pm$ 5.0	11.0 $\pm$ 4.8	15.1 $\pm$ 4.3	4.0 (3.0; 5.1)	<0.001
Physical fatigue	11.4 $\pm$ 4.8	9.9 $\pm$ 4.9	13.0 $\pm$ 4.1	3.1 (2.1; 4.2)	<0.001
Reduced activity	10.2 $\pm$ 4.6	8.8 $\pm$ 4.1	11.6 $\pm$ 4.6	2.8 (1.8; 3.9)	<0.001
Reduced motivation	9.8 $\pm$ 4.2	8.6 $\pm$ 3.8	11.0 $\pm$ 4.4	2.3 (1.4; 3.3)	<0.001
Mental fatigue	11.1 $\pm$ 5.1	9.5 $\pm$ 4.8	12.7 $\pm$ 4.9	3.0 (1.9; 4.2)	<0.001

AIH, autoimmune hypothyroidism; DTC, differentiated thyroid carcinoma; ND, not determined.

^a χ^2 test for gender, independent samples *t*-test for age and thyroid parameters. Differences in MFI-20 scores were tested in a linear regression model, after adjustment for age and gender.

^bAfter log transformation of TSH levels.

higher L-T₄ dose. DTC patients had significantly lower T₃ levels (1.56 vs 1.72 nmol/l).

Patients with AIH had significantly higher fatigue scores than DTC patients ($P < 0.001$), reflected by higher scores on all five MFI-20 subscales. Regression analysis showed that the effect of disease status (DTC vs AIH) on fatigue scores was not materially changed after adjustments for differences in thyroid parameters (FT₄, TSH, T₄, and T₃) or general characteristics (BMI, age, or gender).

TSHR-Asp727Glu genotype status and thyroid parameters

In the total study population, the frequency of the TSHR-Glu727 allele was 7.2% (Table 2). Distribution of genotype frequencies (Asp/Asp 85.6%, Asp/Glu 14.4%, Glu/Glu 0%) showed no deviation from Hardy–Weinberg equilibrium ($X^2 = 1.67$; $P = 0.20$). Stratified by diagnosis (DTC vs AIH) also, no deviation from Hardy–Weinberg equilibrium was shown. In AIH patients, the Asp/Glu genotype frequency was slightly higher than in DTC patients (18.1 vs 10.7%).

In the total study population, heterozygous patients (45.1 years) were younger than wild-type patients (49.4 years). Heterozygotes and wild types had similar FT₄ (18.2 vs 18.1 pmol/l) and TSH levels (0.60 vs 0.42 mU/l). T₃ levels were higher in heterozygous than in wild-type patients (1.80 vs 1.61 nmol/l; $P = 0.006$), despite similar serum T₄ and FT₄ levels. T₄ dose did not differ between genotypes.

In DTC patients, no significant differences in clinical and biochemical parameters between genotypes were observed. Duration of cure, initial tumor stage, total radioiodine dose, recurrence frequency, and relative number of patients who had undergone a modified radical neck dissection were comparable between wild types and heterozygotes. Heterozygous AIH patients had significantly lower serum TSH levels than wild-type AIH patients (0.89 vs 1.40 mU/l) and concomitantly higher serum T₃ levels (1.83 vs 1.69 nmol/l).

MFI-20 scores by TSHR-Asp727Glu genotype

In the total study population ($n = 278$), average MFI-20 scores were slightly lower in four of five subscales in heterozygous patients, indicating less fatigue in these subjects. However, in none of the five subscales (general fatigue, physical fatigue, reduction in activity, reduction in motivation, and mental fatigue), the difference was statistically significant after adjustment for age and gender.

Joint effects of genotype status and disease on fatigue: interaction analysis

In order to determine whether the effect of genotype on fatigue varied according to the cause of hypothyroidism (DTC vs AIH), an interaction analysis was performed (Fig. 2).

Table 2 Baseline characteristics and thyroid hormone parameters by TSHR-Asp727Glu polymorphism genotype status. Data are expressed as mean $\pm$ s.d., median (range), or percentage as appropriate.

Genotype	Patients (n)	Age (years)	Sex (female, %)	BMI (kg/m ²)	T ₄ dose (μ g/kg)	FT ₄ ^a (pmol/l)	TSH ^a (mU/l)	T ₄ ^a (nmol/l)	T ₃ ^a (nmol/l)
Total study population ($n = 278$)									
WT (Asp/Asp)	238	49.4 $\pm$ 11.7	85.3	27.1 $\pm$ 5.6	1.88 $\pm$ 0.89	18.1 $\pm$ 4.8	0.42 (0.01–6.50)	134.9 $\pm$ 7.2	1.61 $\pm$ 0.37
HeZ (Asp/Glu)	40	45.1 $\pm$ 9.0	75.0	27.6 $\pm$ 5.9	1.86 $\pm$ 0.84	18.2 $\pm$ 5.3	0.60 (0.02–5.90)	143.9 $\pm$ 5.9	1.80 $\pm$ 0.39
Mean differences (95% CI)		–4.3 (–8.1; –0.5)	ND	0.4 (–1.5; 2.3)	–0.02 (–0.32; 0.28)	0.1 (–1.5; 1.8)	0.14 ^b (–0.46; 0.74)	9.1 (–4.4; 22.5)	0.18 (0.05; 0.32)
P value ^c		0.027	0.102	0.664	0.878	0.875	0.648 ^b	0.186	0.006
DTC ($n = 140$)									
WT (Asp/Asp)	125	49.7 $\pm$ 12.9	82.4	25.7 $\pm$ 4.6	2.15 $\pm$ 0.97	21.3 $\pm$ 3.9	0.07 (0.01–5.35)	148.1 $\pm$ 43.7	1.54 $\pm$ 0.42
HeZ (Asp/Glu)	15	45.8 $\pm$ 11.6	73.3	26.0 $\pm$ 3.2	2.28 $\pm$ 1.09	22.8 $\pm$ 5.2	0.09 (0.02–2.82)	169.2 $\pm$ 58.2	1.72 $\pm$ 0.44
Mean differences (95% CI)		–3.9 (–10.8; 3.0)	ND	0.3 (–2.2; 2.8)	0.14 (–0.41; 0.69)	1.5 (–0.7; 3.7)	0.21 ^b (–0.64; 1.07)	21.1 (–6.1; 48.3)	0.19 (–0.07; 0.44)
P value ^c		0.268	0.394	0.804	0.618	0.185	0.622 ^b	0.128	0.151
AIH ($n = 138$)									
WT (Asp/Asp)	113	49.1 $\pm$ 10.2	88.5	28.8 $\pm$ 6.2	1.58 $\pm$ 0.67	14.6 $\pm$ 2.8	1.40 (0.05–6.50)	121.7 $\pm$ 22.9	1.69 $\pm$ 0.31
HeZ (Asp/Glu)	25	44.7 $\pm$ 7.2	76.0	28.5 $\pm$ 6.9	1.62 $\pm$ 0.55	15.5 $\pm$ 3.0	0.89 (0.04–5.90)	131.8 $\pm$ 33.7	1.83 $\pm$ 0.37
Mean differences (95% CI)		–4.4 (–8.7; –0.2)	ND	–0.3 (–3.1; 2.4)	0.03 (–0.3; 0.3)	0.9 (–0.3; 2.2)	–0.5 ^b (–0.9; 0.0)	10.1 (–0.9; 21.1)	0.14 (0.0; 0.3)
P value ^c		0.014	0.101	0.816	0.827	0.139	0.038 ^b	0.165	0.044

AIH, autoimmune hypothyroidism; DTC, differentiated thyroid carcinoma; ND, not determined.

^aSerum T₄ and serum T₃ were available in 262 patients (total group = 262 patients (Asp/Asp = 225; Asp/Glu = 37), DTC = 124 patients (Asp/Asp = 112; Asp/Glu = 12) AIH = 138 patients (Asp/Asp = 113; Asp/Glu = 25) in which genotyping and MFI-20 scores were determined. Serum FT₄ and serum TSH were available in 277 patients (total group = 277 patients (Asp/Asp = 237; Asp/Glu = 40); DTC = 139 patients (Asp/Asp = 124; Asp/Glu = 15); AIH = 138 patients (Asp/Asp = 113; Asp/Glu = 25) in which genotyping and MFI-20 scores were determined.

^bAfter log transformation of TSH levels.

^c χ^2 test for gender and independent samples *t*-test for all other variables.

Wild-type DTC patients were set as the reference category and all analyses were adjusted for age and gender.

Compared with wild-type DTC patients, heterozygous DTC patients had lower scores on four of five MFI-20 subscales: general fatigue (MD -4.2 ; 95% CI $-6.5, -1.8$), physical fatigue (MD -3.9 ; 95% CI $-6.3, -1.5$), reduction in activity (MD -1.6 ; 95% CI $-4.0, 0.7$), and reduction in motivation (MD -1.8 ; 95% CI $-4.0, 0.4$), corresponding to $\sim 20\%$ lower scores on general fatigue and physical fatigue and 10% lower scores on the other two subscales.

Wild-type AIH patients scored clearly higher on all five MFI-20 subscales compared with wild-type DTC patients ($P < 0.001$): general fatigue (MD 3.7 ; 95% CI

$2.6, 4.8$), physical fatigue (MD 2.9 ; 95% CI $1.7, 4.0$), reduction in activity (MD 2.7 ; 95% CI $1.5, 3.8$), reduction in motivation (MD 2.3 ; 95% CI $1.3, 3.4$), and mental fatigue (MD 3.1 ; 95% CI $1.9, 4.4$). Heterozygous AIH patients had similar MFI-20 scores as wild-type AIH patients.

Formal interaction analysis showed a less than additive effect of the TSHR-Asp727Glu polymorphism on MFI-20 scores in AIH patients in two subscales: general fatigue ($P = 0.02$) and physical fatigue ($P = 0.046$). Adjustment for thyroid parameters or BMI did not change these study results materially.

Discussion

This study evaluated the relationship between fatigue and origin of hypothyroidism in a population of 278 patients on thyroid hormone treatment therapy for different causes of hypothyroidism. In our study, fatigue and fatigue-related symptoms were more pronounced in AIH patients compared with DTC patients, reflected by significantly higher scores on all five MFI-20 subscales. As AIH patients were more obese and had a different thyroid hormone profile, results were adjusted for BMI and thyroid parameters, which did not alter study results. Therefore, our findings probably represent a disease-specific decrease in quality of life. Compared with data from the general population, AIH patients, but also DTC patients, reported more fatigue-related symptoms (33). Patients with other autoimmune diseases (i.e. Sjögren's syndrome and rheumatoid arthritis) have similar low MFI-20 scores as we found in the AIH population (33). The disease-specific effect in AIH patients may be explained by autoimmunity. Recently, it was documented that complaints of fatigue in patients with Hashimoto's thyroiditis with elevated anti-TPO antibodies are related to autoimmunity as such rather than thyroid function (34). The indication for thyroid function tests in AIH patients may be fatigue, which may cause overrepresentation of fatigued patients among all patients with AIH. Albeit, fatigue status was determined in patients on thyroid hormone replacement therapy for a longer period in a steady state of euthyroidism and not immediately after diagnosis of hypothyroidism.

In our study, a modest impact of the TSHR-Asp727Glu polymorphism on fatigue was found in DTC patients only, an effect not seen in the more fatigued AIH patients. This finding should be interpreted with caution and replication is needed in order to establish a role of the TSHR-Asp727Glu polymorphism on fatigue-related symptoms in DTC patients with more certainty. It should also be emphasized that the study might be underpowered to detect a small effect of the polymorphism on fatigue-related symptoms in the total study population.

The TSHR-Glu727 variant has been proposed to have higher sensitivity for TSH than the wild-type variant

Figure 2 Joint effect of TSHR-Asp727Glu polymorphism and disease status on MFI-20 scores. MFI-20 scores by disease and genotype status are presented. Asterisks (*/**/****) denote P values corresponding to the difference with the reference group (DTC + WT). All MFI-20 scores were adjusted for age and gender. WT, wild-type; HeZ, heterozygous; DTC + HeZ ($n = 15$); DTC + WT ($n = 125$); AIH + HeZ ($n = 25$); AIH + WT ($n = 113$).

because less TSH is required to maintain normal FT₄ serum levels (19, 20, 21). TSH-suppressed DTC patients might have better conditions for an advantageous effect of a TSHR variant with an increased sensitivity because in a state of lower serum TSH concentration, a more sensitive TSHR could attribute to efficient local TSH effects. However, the functional significance of the TSHR-Asp727Glu allele has not yet been disentangled in all details (35, 36, 37). A TSHR-mediated mechanism was proposed to be involved in stimulation of D2 expression by TSH in rat astroglial cells, cultured rat brown adipose tissue, and human osteoblasts (7, 8, 15). D2 plays an important role in maintaining local bioavailability of thyroid hormone by catalyzing conversion of T₄ to T₃ (25). Because patients on replacement therapy with L-T₄ are presumably more dependent on deiodinase activity in peripheral tissue for their T₃ production, extrathyroidal D2 enzyme activity in these patients could be of higher relevance than in non-diseased subjects. Given that expression of TSH mRNA has been reported in human brain (12, 14), an analogous positive role of TSH on D2 levels in human brain areas may be plausible. On the other hand, D2 expression in the human brain is highly localized and restricted to selective cell types such as hypothalamic tanycytes and additional non-neuronal cells (38). Interestingly, folliculostellate cells in the human anterior pituitary express both D2 and TSHR (39), but no data are available at present about neuronal or glial D2 and TSHR co-expression in human brain. TSHR activity may also affect other intracellular pathways, independent of intracellular T₃ content.

Thyroid hormone profile differed substantially between DTC and AIH patients, reflected by significantly lower serum TSH and T₃ levels in DTC patients on thyroid hormone suppression therapy. The significantly lower serum T₃ levels may reflect the inhibition of deiodinase activity due to supranormal synthetic thyroid hormone dose (40). The TSHR-Asp727Glu allele was associated with higher serum T₃ levels in our study population, which may support the concept of D2 stimulation by a TSHR-mediated mechanism (7, 8, 15).

A large British community-based survey showed that patients on thyroid hormone replacement therapy for hypothyroidism due to different causes, with TSH and thyroid hormone levels in the normal RR, had considerably worse scores on psychological well-being, compared with their sex- and age-matched controls not on thyroid hormone treatment (1). Similarly, impaired neurocognitive functioning in hypothyroid patients has been described (2, 41). These findings emphasize the importance of research on determinants of well-being in patients with hypothyroidism.

In conclusion, this study demonstrated that patients with AIH were significantly more fatigued in contrast to patients with hypothyroidism after total thyroidectomy, which could not be attributed to thyroid or clinical parameters. A small and favorable effect of the

TSHR-Asp727Glu polymorphism on fatigue and fatigue-related symptoms was found in thyroidectomized patients treated for thyroid carcinoma. This effect could not be found in patients with hypothyroidism due to autoimmune. Replication of these results is warranted.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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