MECHANISMS IN ENDOCRINOLOGY

Impact of isolated TSH levels in and out of normal range on different tissues

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Abstract

Routine treatment of thyroid cancer (TC) includes long-term suppression of TSH. The necessity of this treatment in low- and intermediate-risk patients as well as the extent of TSH suppression is currently under discussion. A literature search was performed to illustrate the role of TSH in extrathyroidal cells and to identify potential reasons for different effects of exogenously suppressed and endogenously low TSH levels. Although adverse effects of subnormal and supranormal TSH blood levels on heart and brain have not been consistently found, studies show a clear negative effect of suppressed TSH levels on bone mineral density. Experimental data also support an important role of TSH in the immune system. The ability of levothyroxine (L-T₄) to regulate TSH levels and triiodothyronine levels in a physiological manner is limited. Reduction of circadian changes in TSH levels, decrease of thyroid hormone-binding proteins, prevention of potential compensatory increases of TSH levels (e.g., in old age), and unresponsiveness of TSH-producing cells to TRH on L-T₄ treatment might cause adverse effects of suppressed TSH levels. In view of the adverse effects of aggressive TSH suppression, achieving the suggested levels of TSH between 0.9 and 1 mU/l in the treatment of low-to-intermediate risk TC patients appears justified.

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Introduction

Thyroid cancer (TC) is the most frequent endocrine malignancy worldwide. A recent study reported that its incidence is increasing in all countries, except in Africa, and that TC incidence has decreased recently only in a few countries (Norway, Sweden) (1). The general increase appears to be due to earlier detection, lack of a decrease in mortality, and increased exposure to radiation and other environmental carcinogens. Furthermore, exposure to some chemicals during intrauterine life and early childhood might induce epigenetic changes and promote mutagenesis. Differentiated TC represents more than 90% of all TC; papillary TC followed by follicular TC are the most common types, representing 80% and 10–20%, respectively, of these tumors (2). Patients with papillary

TC have the best 5-year survival rate (>97%), with survival rates for follicular TC being only slightly worse (91%). Routine treatment of these tumors includes surgical removal of the thyroid gland followed by radioiodine therapy. TC with a low risk of progression and recurrence includes classic papillary TCs without local or distant metastases, complete resection of the tumor, no vascular invasion, and no radioiodine uptake outside the tumor region (3). Intermediate risk tumors have microscopic extrathyroidal extension, cervical lymph node metastases, aggressive histology, and vascular invasion. High risk tumors are characterized by gross extrathyroidal extension, incomplete tumor resection, distant metastases, and inappropriate thyroglobulin elevation. To prevent

recurrence, suppression of thyroid-stimulating hormone (TSH) levels by substitution with levothyroxine (L-T₄) is recommended, according to the Thyroid Cancer Treatment Protocols (4): 'TSH suppression to <0.1 mU/l is indicated in intermediate- and high-risk disease. TSH maintenance at or slightly below the lower-normal limit (0.3–2 mU/l) may be considered for low-risk disease'. After 5–10 years of follow-up, if serum thyroglobulin is undetectable and there is no clinical evidence of disease, a TSH level of 1.0–2.0 mU/l is advisable in high-risk TC patients (5).

Meta-analysis of 28 studies reported a correlation of TSH-levels and incidence of TC. The odds ratio (OR) increased with 1.72 per mU/l when TSH levels were <1 mU/l and with 1.16 per mU/l for TSH levels ≥1 mU/l (6). This association provided the theoretical basis for recommending suppression of TSH in TC patients, but the advantage of this treatment has not been convincingly shown. Disease-free survival in papillary TC was <10% worse in patients with suppression treatment than in those without (7). Other reports did not indicate any effect of suppression on the outcome of patients with differentiated TC (8). These data are in agreement with a recent study that showed no advantage of TSH suppression in low-moderate risk TC patients in terms of tumor recurrence and disease-free survival over 6.5 years (9). In that study, patients with ≤0.4 mU/l were classified as suppressed and >0.4 mU/l were taken as not suppressed. Recurrence rates did not differ between the groups (6% in the suppressed and 4.5% in the not suppressed). Osteoporosis, on the other hand, was 3.5-fold higher in women of all ages and 4.3-fold higher in elderly women with TSH suppression. The risk for atrial fibrillation was also increased in the suppressed group, although only to a slight extent.

The increased risk of adverse effects in the absence of significantly improved disease-free survival and lack of recurrence question the advantage of suppression therapy in TC. This review aims to summarize current knowledge on the effects of TSH in different cell types. TSH levels and TSH receptor expression in normal and diseased individuals are compared to identify mechanisms that may explain the higher rate of adverse effects in patients with suppressed TSH levels compared to subjects with low, normal, or increased TSH levels. Furthermore, the effects of abnormal TSH levels on bone, the heart, the brain, and the immune system are discussed. Finally, TSH receptor expression and its role in cancers other than TC are addressed.

Structure and signaling of the TSH receptor

The TSH receptor is similar in composition to the rhodopsin G protein-coupled receptors (GPRs) for follicle-stimulating hormone and luteinizing hormone/choriogonadotropin (10). The receptor consists of a seven-transmembrane (serpentine) domain and has a large 400 amino acid extracellular NH₂ domain with N-glycosylation sites and leucine-rich repeats and cysteine clusters. It is hypothesized that the extracellular domain of the TSH receptor exerts an inhibitory action; receptors lacking the extracellular domain are functional and show a low level of activation. Upon binding of TSH, signaling is raised above this background activity. The COOH terminus of the receptor is located intracellularly (Fig. 1). The receptor is a trimer consisting of α , β , and γ subunits. On activation, $\beta\gamma$ separate from the α subunit and effects are mediated by G α s and G α q subunits. The released and activated $\beta\gamma$ complex serves as a docking site for interaction with downstream effectors of the signal transduction cascade of G-proteins. The G α s complex initiates signaling by the protein kinase A (PKA)–CREB or by activating the MEK1/2/ERK/Elk1 pathway (11). The G α q pathway mediates activation of phospholipase C and leads to the formation of phosphatidylinositol 3,4,5 triphosphate and Akt activation. Diacylglycerol activates PKC and acts either via NF κ B or via c-RAF and ERK1/2 (Fig. 1). In addition to the thyroid, TSH receptor expression has been demonstrated

Figure 1

Structure of the TSH receptor and signaling pathways according to Morshed *et al.* (11). AC, adenylyl cyclase; DAG, diacylglycerol; PKC, protein kinase C; PLC, phospholipase; PI3K, phosphatidylinositol 3,4,5 triphosphate; PKA, protein kinase; ICS, intracellular space; ECS, extracellular space.

in a variety of tissues such as the anterior pituitary gland, hypothalamus, ovary, testis, skin, kidney, immune system, bone marrow, peripheral blood cells, adipose tissue, orbital preadipocyte fibroblasts, and bone (12). The level of cellular TSH receptor expression, receptor gene polymorphisms, and existence of splice variants influence the biological activity of a given TSH concentration. Cellular receptor expression is correlated with lower TSH affinity suggesting negative cooperation (13). Heterozygous individuals with TSHRAsp727Glu polymorphism inducing a gain-of-function have increased bone mineral density (BMD) and bone mineral content. These individuals usually have reduced TSH levels but increased cAMP response to TSH receptor stimulation (14). TSH β splice variants have been described in immune cells, where they play a role in the suppression of thyroid hormones in the initial phase of infections (15). According to animal studies, the dys-balance of the ratio of native TSH β /TSH β splice variants might be involved in the pathogenesis of several inflammatory and autoimmune diseases (16). However, the presence of the TSH β splice variant has not been confirmed in human bone marrow cells (17).

Role of TSH in TC

Several studies indicate that TSH plays a role in proliferation of TC cells (18, 19, 20) and in the first phase of tumorigenesis (21). The evidence for this comes from *in vitro* studies, animal studies, and clinical data. TSH can promote progression of TC by stimulating the secretion of vascular endothelial growth factor (VEGF) to induce neo-angiogenesis (22), and TSH signaling confers more aggressive features in BRAF(V600E)-induced thyroid tumors in mice (23). In patients with nodular disease, an association of low TSH values and lower TC rates has been reported (24). However, the idea of TSH as a stimulator of TC cells is questioned by the fact that TC cells are relatively insensitive or resistant to TSH stimulation, and expression levels of the TSH receptor are significantly lower in carcinoma tissues than in normal tissues. Furthermore, in contrast to normal thyrocytes, TSH signaling through cAMP acts as a negative regulator in TC cells (25). Finally, the effect of TSH on TC cells is biphasic, with proliferative effects at low concentrations and anti-proliferative action at higher concentrations, at least *in vitro* (26). It is not clear to which extent this dose dependency is relevant for patients because the cell culture experiments used relatively high concentrations of TSH from nonhuman sources. It is very likely that TSH is not the only regulator of TC physiology because other growth factors, mainly

TGF α and VEGF, can take over the pro-angiogenetic action of TSH (27).

Regulation of TSH secretion

Thyroid disorders are identified by measurements of TSH levels as well as free thyroxine (FT₄) and triiodothyronine (T₃). Only 0.03% of T₄ and 0.3% of T₃ circulate in the free form, but TSH and FT₄ are routinely used to assess thyroid function and to monitor hyper- and hypothyroidism treatment. FT₄ is not susceptible to changes in the expression of thyroid hormone-binding proteins in the blood and has little intra-individual variability. TSH levels in blood reflect the steady state achieved after 6–8 weeks of T₄ treatment, and FT₄ testing reports the most recent adjustments in T₄ (28). Like many other pituitary hormones, TSH has a pulsatile and variable secretion pattern. Reported circadian patterns of TSH blood levels show a similar shape in normal adults and in lean and obese women (29, 30, 31). Maximum values of around 2.5 mU/l were measured in studies on a population of normal men and women (green and blue curves, Fig. 2). By contrast, levels in lean women were ~0.5 mU/l lower (continuous vs dotted line pink curve, Fig. 2).

Maximum TSH levels, circadian rhythm, and pulses of TSH secretion are influenced by sleep, age, season, and fasting (32, 33, 34) but are not strongly dependent on age, sex, and body weight (35). TSH values measured in 324 750 healthy individuals at different times of the day confirmed the dependence on sex, age, and time of blood collection (36). The authors pointed out that the time of

Figure 2

Comparison of TSH blood levels from healthy individuals and lean women according to three different studies, taken as examples (29, 30, 31). The study of Kok *et al.* (29) differentiated between lean and obese women; TSH levels of lean women are presented as a continuous line and TSH levels of obese women as a dotted pink line.

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blood collection in the morning may not correspond to the biological clock of individuals with shift work, sleeping disorder, or jet lag. Taking time of collection, age, and sex into account, TSH levels up to 7.5 mU/l are in the normal range. Furthermore, the degree of TSH suppression in the morning might not correspond to the same extent of suppression during the night, and ingestion of L-T₄ in the morning results in lower suppression than medication in the afternoon (37). Moreover, comorbidities alter TSH levels, which are increased after recovery from major illness, obesity, adrenal insufficiency, medication, and renal failure (38). TSH levels increase in older subjects, particularly in women, whereas no changes have been observed in elderly men (39). Increases in TSH levels in old age could be a consequence of age-related alteration in the TSH set point or reduced TSH bioactivity (40). The Leiden 85+ study revealed an association of low thyroid activity (high TSH levels) with longevity (41). Higher TSH levels in a population of Ashkenazi Jews with exceptional longevity appear to support the correlation of increased TSH levels, low thyroid function, and long life (42). While those studies suggest correlations of increased levels with longevity, other studies do not report any association of increased TSH-levels and long life (43). Under the assumption that the increase in TSH levels is a physiological reaction to adapt to lower expression or sensitivity of TSH receptors, artificial suppression could potentially have negative effects.

TSH levels are altered in subclinical hypothyroidism (SCH) and subclinical hyperthyroidism (SH), both of which are usually asymptomatic pathologies characterized by free (F) T₃ and T₄ levels in the normal range and increased TSH levels in SCH and decreased TSH levels in SH. SCH has a prevalence of 4–9.5% and an endogenous origin, while SH is due to endogenous (5.5–6.5%) and exogenous (10.9%) causes (44). Reduced TSH levels in nontoxic goiter showed night/day differences and only slightly lower TSH pulses (32). In SH, circadian rhythms of TSH levels are preserved down to 0.005 mU/l, while night/day differences in TSH disappeared at 0.002 mU/l (45, 46). Similarly, decreased basal and pulsatile TSH secretion but retained rhythmic changes were detected also in active acromegaly, which is not accompanied by increased bone fragility (47, 48). This rhythmicity, on the other hand, was almost completely lost in Alzheimer's disease (49) and might contribute to the increased fracture rate and osteoporosis of still very mobile patients in the early stages of Alzheimer's disease (50). Increased cellular stress and oxidative signaling by the NFκB pathway appear

to be involved in the etiology of osteoporosis (51). TSH receptor signaling and cellular stress and TSH receptor activation could interact at the level of NFκB activation (Fig. 1). TSH receptor expression in rats is subject to diurnal changes with the lowest levels during the day and the highest levels at night, when TSH levels are also highest (52). The finding that intermittent TSH application promotes bone formation in patients supports the hypothesis that a certain extent of fluctuations in TSH levels might be essential for normal bone physiology (53). In hypothyroid patients under therapy with T₃, T₄, or T₃/T₄ aiming to achieve euthyroidism, absolute TSH levels and circadian variations were reduced but not absent (37, 54, 55). However, loss of response to thyrotropin-releasing hormone (TRH) was observed in almost all TC patients treated with thyroid hormone for suppression of TSH levels (56, 57). Lack of response to TRH was linked to the development of osteoporosis (58), but the mechanism is currently unknown.

TSH levels are regulated by TRH and T₄ and T₃ levels (59). The iodothyronine deiodinases types I, II, and III (D1, D2, and D3) play an important role in this process. These enzymes regulate thyroid hormone activity via removal of a specific iodine moiety from T₄. D2 activates and D3 inactivates T₃, and D1 can have both effects (59). Long-term TSH suppression (3 years) has been shown to decrease levels of total T₄ and T₃ in serum samples from differentiated TC patients (60). The ratio of total T₄:T₃ was increased and the authors speculated that down-regulation of D1 and D2 and upregulation of D3 were the underlying causes of the observed changes. Altered total T₃:T₄ ratios usually result from changes in transport proteins, not thyroid function (28). Because the affinity of thyroxine-binding globulin (TBG) for T₄ is higher than for T₃ (61), the observed changes may reflect a decrease of TBG levels under therapy. Experimental hyperthyroidism caused decreases of TBG levels, whereas experimental hypothyroidism increased them in rhesus monkeys (62). These results appear to indicate that effects of TSH suppression could also be related to changes of TBG levels.

In addition to average TSH levels and amplitude of TSH pulses, the extent of glycosylation regulates the biological activity of TSH (63). Hypothyroidism is associated with increased sialylation and lower biological activity. The authors suggested that the increase in circulating TSH levels in hypothyroid patients compensates for the decreased biological activity. The sialylation pattern shows circadian changes and is high at night and low during the day (64). Glycosylation is regulated by

T₄ and treatment of hypothyroidism with L-T₄ normalized the sialylation pattern (65).

Difficulties in finding the right dose of L-T₄ for TSH suppression may also explain the increased rate of adverse effects under TSH suppression. A given dose of exogenous T₄ induced TSH suppression in 51.1%, normal levels in 44.4%, and elevated levels in 4.5% of goiter and TC patients (66). On the other hand, FT₄ was elevated in 30.4% but normal in 69.6% of patients with suppressed TSH levels (67). Variations cannot be explained by low and variable absorption in the intestine (68), dependence on the fasted or sated condition (69), difference in lean body mass (70), or more rapid excretion. The half-life of T₄ is quite long (6–7 days for euthyroid, 9–10 days for hypothyroid, and 3–4 days for hyperthyroid individuals) and enables maintenance of suppressed TSH levels when medication is only taken every other day (71). Variable effects of L-T₄ dosing appear to be due to deficiency in regulation of T₃ homeostasis in patients under T₄ replacement and suggest that the interplay between free T₃ (FT₃) and both pituitary and peripheral TSH is dysregulated (72, 73). The authors identified significantly lower FT₃ levels in patients with SCH treated with L-T₄ vs patients without treatment. In the treated patients, TSH levels were lower and FT₄ levels higher; FT₃ levels closely correlated with the L-T₄ dose. In untreated patients, TSH levels regulated FT₃ levels, which were stable over a wide range of circulating TSH levels (0.2–7 mU/l). The authors identified reduced deiodinase activity due to impaired or absent thyroid function as the reason for these observed alterations. These findings question the use of TSH levels as a reliable parameter for the correct dosing of T₄.

Role of TSH in bone

Thyroid hormones and bone turnover are closely related as major factors for the resistance of bone to fracture. The bone remodeling cycle takes 150–200 days in euthyroid individuals, half of that time in hyperthyroid patients, and around 700 days in hypothyroid subjects (74). Several studies support the hypothesis that increased free (F) T₃ and T₄ levels are less important for the observed pathology than TSH levels. Hyperthyroid women with TSH levels <0.1 mU/l were more affected than women with TSH levels >0.5 mU/l (75). Unfortunately, this study does not allow discrimination between TSH effects and contribution of increased free (F) T₃ and T₄ levels because these data were only measured in the population with TSH levels <0.2 mU/l and were not analyzed. In a survey on TSH levels within the reference range and bone status in

postmenopausal American women, Morris (76) reported that BMD increased significantly as TSH increased in both black and white women. Furthermore, the OR relating levels of TSH 0.39–1.8 mU/l vs 1.8–4.5 mU/l to osteoporosis and osteopenia were 3.4 and 2.2 respectively. The positive effect of TSH on bone formation has further been demonstrated in a case study on normal bone formation after TSH substitution in two boys suffering from isolated TSH deficiency due to a mutation of the TSH β -subunit gene (77).

Numerous other studies have evaluated the action of TSH on bone mass and quality but have yielded discrepant results. Bone quality is not precisely defined and includes all of the factors that determine how well the bone resists fracturing (78). Microarchitecture, accumulated microscopic damage, collagen quality, and mineral crystal size all influence bone quality. Mineral density and bone strength can be discordant, and a lack of change in bone density in patients taking bisphosphonates does not necessarily indicate a lack of response. One meta-analysis of 31 studies reported partial negative and/or positive effects of suppressed TSH levels on bone mass in 23 studies and exclusively negative effects in the other nine. In a second evaluation, only clinical trials that fulfilled specific requirements regarding design, conduct, and analysis of the trial and reporting were included. When only the high quality studies were included, three reported no effect, four mixed effects, and three overall negative effects (79). Another meta-analysis of five higher quality studies excluding L-T₄ recipients found that the risk for hip fractures had a hazard ratio of 2.16 for SH and 1.12 for SCH (80). While low TSH levels were linked to increased bone turnover and decreased bone density, supranormal TSH levels reduced bone quality without affecting mineralization (81). Suppression of TSH levels was the main reason for the observed effect because patients with FT₄ levels in the upper normal range and normal TSH-levels did not present with decreased bone density. Another observation also supports the lack of physiological replacement by exogenous T₄. When TSH levels in patients with SCH were lowered by L-T₄ treatment, normal bone structure could not be restored (82). TSH suppression for TC showed similar results as TSH suppression for SH and was accompanied by increased bone resorption in postmenopausal women (83). It has been shown that a 50% reduction of TSH receptors on osteoclast precursors induced osteoporosis (84). Conversely, low TSH levels *per se* did not diminish bone quality, supporting the hypothesis that levels of TSH alone might not be associated with osteoporosis (85).

Effects on bone have been described mainly in postmenopausal women, highlighting the role of estrogen that has direct and indirect effects on thyroid physiology. For instance, estrogen increases TBG levels, which reduces the amount of FT₄ in the blood. Furthermore, activation of estrogen receptors alpha and beta or of the GPR30 regulated proliferation of thyrocytes (86). Lack of estrogen following gonadectomy in rats decreased circulating TSH levels and thyrocyte TSH receptor expression (87). Prevention of bone loss also depends on a sufficient supply of estrogen, which exerts effects on osteocytes and osteoclasts. A lack of estrogen induced apoptosis of osteocytes, prevented their stimulation by mechanical strain, and stimulated receptor activator of nuclear factor kappa B (RANK) signaling in osteoclasts (88). Osteoclasts originate from multipotent progenitors in the bone marrow and differentiate to pre-monocytes. After differentiation to osteoclast precursors, they fuse and become mature (multinucleated) osteoclasts. RANK ligand (RANKL) is the primary mediator of the differentiation from osteoclast precursors to osteoclasts (Fig. 3). RANKL binding to its cellular receptor mediates maturation and activation of osteoclasts. The sensitivity of osteoclasts to TSH is regulated by estrogen, a lack of which causes the bone loss observed in postmenopausal women under TSH suppression with l-T₄ (89). Both estrogen binding to estrogen receptor alpha and TSH binding to TSH receptors inhibit RANKL signaling (90) and bone degradation. Estrogen acts by increasing osteoprotegerin, which binds RANKL and prevents it from binding to RANK (Fig. 3), while TSH receptor activation can antagonize RANKL signaling. TSH can increase bone mass in ovariectomized rats by inhibition of RANKL-induced osteoclast formation and stimulation of osteoblast differentiation (91).

Role of TSH in the cardiovascular system

Patients with differentiated TC showed a higher risk for cardiovascular mortality, and low TSH levels predicted cardiovascular mortality (92). Minor thyroid dysfunction (SCH and SH) has no effect on total and cardiovascular mortality in older men (93). A recent study of 55 412 individuals with a median follow-up from 3.3 to 20.0 years showed that TSH levels of 0.4–4.49 mU/l were not associated with an increased frequency of cardiovascular events and cardiovascular mortality (94). Lower TSH levels (<0.1 mU/l), however, were associated with cardiovascular problems and accompanied by a modest increase in mortality of older, but not middle-aged, people (95).

Figure 3

Role of RANKL and TSH in osteoclast maturation. Osteoclast precursors mature when receptor activator of nuclear factor kappa B ligand (RANKL) binds to its receptor (RANK) together with activation of the macrophage colony-stimulating factor (M-CSF) receptor. When RANKL is bound to osteoprotegerin (OPG), no activation can take place. In the mature osteoclast, survival, differentiation, and activation are maintained via activation of NFκB, MAPKs, and Akt. Binding of TSH to its receptor (TSHR) antagonizes RANKL signalling via inhibition of all pathways. N, nucleus.

Elderly people with low TSH experience cardiovascular complications (atrial fibrillation) more frequently than individuals with normal TSH levels and patients older than 60 years have a higher prevalence of atrial fibrillation on TSH suppression (12, 96). Subclinical thyroid dysfunction remains a controversial issue. SCH is associated with impaired left ventricular diastolic function at rest, systolic dysfunction on effort, and enhanced risk for atherosclerosis and myocardial infarction (97) and is linked to increased coronary heart disease and mortality risk especially for those having a TSH > 10 mU/l and who are

younger than 65 years (98, 99). Application of recombinant TSH in patients with differentiated TC reduced endothelium-dependent vasodilation and induced pro-inflammatory reactions at the endothelium and increased markers of oxidative stress (100). Subjects with SCH present with increases in LDL-cholesterol, diastolic blood pressure, C-reactive protein and angiotensin receptor expression, and decreased nitric oxide (NO) levels (101). In cellular studies, TSH promoted tumor necrosis factor alpha (TNF α)-induced upregulation of adhesion molecules, decreases of NO synthase and prostacyclin, and increases of endothelin 1 and plasminogen activator inhibitor 1, supporting the hypothesis that TSH promotes endothelial dysfunction (102).

Role of TSH in the brain

Low TSH levels also appear to affect brain function in a negative way. Six of 11 studies reported correlations of dementia and SH or low TSH values and dementia. Furthermore, depression was linked to TSH levels in the lowest normal tertile in women and in elderly people (103, 104). Another study did not find any association between TSH, FT₄, and FT₃ values and depressive symptoms in a rather large, randomly selected population of individuals aged 45–74 years (105). In older people, higher TSH levels are detected more frequently than in younger individuals (42). According to one hypothesis (40), increased TSH levels are the reaction to reduced TSH bioactivity and altered set points. The lack of an age-dependent increase of TSH levels could be the manifestation of a reduced capacity for adaptation in organic brain diseases. Another indication for lack of adaptation in brain diseases was identified in patients with major depression and bipolar disorder in which normal TSH and thyroid hormone levels were seen but responses to stimulation with TRH markedly decreased (106). In contrast to TSH levels, TRH levels do not increase with age (107). On the other hand, increased TSH levels have also been linked to cognitive problems (108). TSH receptor overexpression has been documented in brains of Alzheimer's and Down's syndrome patients (109). The glycosylation pattern of the TSH isoform determines its bioactivity (63), and it is therefore possible that pituitary cells in brain diseases produce a less bioactive TSH molecule. Taken together, the association of abnormal TSH levels and mental disorders is not proven and no association of long-term TSH suppression and cognitive dysfunction has been reported (110).

Role of TSH in the immune system

The relatively high frequency of autoimmune diseases of the thyroid gland suggests a link between the thyroid and immune systems. Asymptomatic autoimmune thyroiditis (Hashimoto's disease) has been identified in postmortem studies in 27% of adult women and 7% of adult men (111). Graves' disease has a prevalence of 0.28–1.2% in women and 0–2% in men (112). Thyroid and thymus also share a common ontogenetic origin (113) and impairments in TSH production in the pituitary gland and immune cells have been shown to occur in parallel (114).

Several effects of TSH on immune cells have been identified so far. TSH supported T-cell development in the thymus (115), enhanced antibody production (116), and improved natural killer cell activity (117). Intraepithelial lymphocyte development in the intestinal epithelium, which does not take place in athymic mice, can be induced by exogenous application of TSH (118). Furthermore, TSH regulated the activity of the intraepithelial immune system on infection with rotavirus (113). The pattern of TSH-immunoreactive cells in the mucosa changed from their presence in the upper and lower parts of the intestinal crypts to the presence of stained cells at the apical region of the villi on infection with rotavirus. On stimulation with TSH, thymocytes responded in a time-dependent manner; application at 0900 h was efficient while application at 1800 h did not induce proliferation (119). This finding underscores the importance of circadian changes in TSH levels and TSH receptor expression, addressed in the section 'TSH levels in healthy subjects'.

TSH receptor expression in other cell types

TSH-receptors are functional in adipocytes, fibroblasts, keratinocytes, and smooth muscle cells. TSH was needed for thermogenesis of *hyt*[−]/*hyt*[−] mice, which do not express TSH receptors and become hypothermic after substitution with T₄, suggesting that both T₄ and TSH are required for thermoregulation (14). The role of TSH for energy consumption in humans is unclear because one study reported a correlation of TSH receptor expression in subcutaneous adipose tissue with BMI (120), whereas another described a negative association of obesity and TSH receptor expression in subcutaneous and visceral adipose tissue (121). Although TSH might not play a prominent role in thermoregulation in humans, it can exert pro-inflammatory effects in human adipose cells (122). The authors showed that recombinant human TSH

elevated serum interleukin 6 (IL6) response in thyroidectomized patients.

Fibroblasts express functional TSH receptors and show induction of IL1, while keratinocytes and smooth muscle cells proliferate after stimulation with TSH (123, 124). Secretion of the proinflammatory ILs IL6, IL8, and TNF α may play a role in Graves' ophthalmopathy (125).

Role of TSH in extrathyroidal cancer

Tumor-promoting effects of thyroid hormones are suspected based on reports of increased tumor formation and metastasis caused by thyroid hormones in animal models (126). Increased incidence of breast cancer in women with higher T₃ levels and its slower progression in patients with hypothyroidism corroborate this hypothesis (127, 128). Cancer incidence has mainly been studied in clinical hypo- and hyperthyroidism in which effects of TSH and abnormal thyroid hormone levels cannot be separated. Hypothyroidism was also correlated with longer survival rates of patients with glioblastoma and head and neck cancer (126). A large study including 115 746 adults in Taiwan reported increased risks of bone, skin, and breast cancer in patients with SCH compared to euthyroid subjects (129). The validity of this association is weakened by the fact that the population with hypothyroidism had higher BMI and higher fasting glucose, cholesterol, and triglyceride levels and that the fraction of smokers and consumers of alcohol and betel nut was higher in this group than in the euthyroid group. Low TSH levels (<0.5 mU/l) increased the risk for prostate and lung cancer compared to the control group with TSH levels in the lower third of the normal range (130). Increased incidence of colorectal cancer might also be associated with low TSH levels because subjects with thyroid hormone replacement were affected more often than individuals with hyperthyroidism and untreated hypothyroidism (131). On the other hand, L-T₄ treatment reduced the risk for colorectal cancer in two other studies (132, 133). Available data do not allow any clear conclusions on the role of abnormal TSH levels on extrathyroidal cancer.

Conclusions

Studies on SCH and SH showed that low TSH levels were associated with more negative effects than supranormal TSH levels. Effects on bone and on cardiovascular and brain function have not been universally found, but decreased bone density in postmenopausal women with suppressed TSH levels was relatively consistently reported. The main factors involved in the adverse effects of TSH

suppression relate to the interaction of TSH and estrogen in osteoclasts, decreased circadian changes in TSH levels, and potentially the lack of response to TRH. Decreases of thyroid hormone-binding proteins on long-term TSH suppression therapy, which resemble changes in experimental hyperthyroidism, may result in hyperthyroidism at the cellular level (62). Lack of correlation between TSH levels and FT₃ levels in L-T₄-treated patients suggests that this cannot compensate for the loss of regulation of FT₃ levels by TSH taking place in the thyroid (73). Furthermore, L-T₄ treatment could not revert endothelial dysfunction, increased blood pressure, cholesterol, and homocysteine levels, hypercoagulability, insulin resistance, and increased frequency of coronary heart disease events induced by supranormal TSH levels (38).

According to current recommendations, TSH levels <10 mU/l in the absence of symptoms do not require thyroid hormone substitution (134). In older individuals (>70 years) even TSH levels >10 mU/l should not be treated unless hypothyroidism or cardiovascular risk is present (135). Treatment of patients with undetectable TSH levels $\leq$ 0.1 mU/l, by contrast, is generally advised to prevent osteoporosis and bone fractures (136, 137). Other authors suggested treatment under the following conditions: hyperactive thyroid dysfunction with nodular origin, goiter, symptoms of thyreotoxicosis, bone- or neuromuscular conditions, gonadal dysfunction, old age, circulating T₃ levels in the upper normal range, and TSH levels <0.01 mU/l (138). Tumor risk has to be taken into account in the treatment of TC patients because studies did not demonstrate a clear advantage of TSH suppression in low- and intermediate-risk TC patients (7, 8, 9). Therefore, there is no need for aggressive suppression of TSH levels in this group of patients. TSH levels of 0.9–1 mU/l are advised for prevention of tumor recurrence (9), while TSH levels should be suppressed for at least 2–5 years in high-risk TC patients (139). In those tumors, TSH suppression shows positive effects on progression of metastatic disease, tumor relapse, and cancer-related mortality (140, 141, 142, 143). In patients with an intermediate risk for TC recurrence and concomitantly a high risk of adverse effects of therapy, the degree of TSH suppression should be reevaluated by a personalized approach during the follow-up period. In elderly patients with DTC and comorbidities, a normal serum TSH is advisable for long-term treatment (8).

Declaration of interest

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

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