ENDOCRINOLOGÍA Y NUTRICIÓN

REVIEW

Potential risks of the adverse effects of thyrotropin suppression in differentiated thyroid carcinoma

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Abstract   In patients with differentiated thyroid cancer, long-term inhibition of TSH secretion by levothyroxine administration is required when there is evidence of persistent or recurrent disease. In such cases, levothyroxine doses should be monitored to achieve the goals of TSH inhibition and avoidance of clinical hyperthyroidism. The possibility that TSH-suppressive therapy may cause adverse effects continues to be controversial, especially for elderly patients. Many studies on the potential harmful effects of suppressive treatment on various organs or systems have been conducted with discordant results. There is however no scientific evidence to suggest that the clinical impact of these effects is significant.

Posibles efectos adversos del tratamiento supresor de la TSH en el carcinoma diferenciado de tiroides

Resumen   En pacientes afectos de cáncer diferenciado de tiroides, la inhibición a largo plazo de la secreción de TSH, mediante la administración de levotiroxina, es necesaria cuando hay evidencias de enfermedad persistente o recurrente. En estos casos las dosis de levotiroxina deben ser monitorizadas para conseguir los objetivos de inhibición de la TSH evitando el hipertiroidismo clínico. La posibilidad de que el tratamiento supresor de la TSH pueda producir efectos adversos es aún motivo de controversia, principalmente en pacientes ancianos. Existen multitud de estudios sobre los posibles efectos perjudiciales del tratamiento supresor sobre diversos órganos o sistemas con resultados discordantes aunque no existen evidencias científicas de que su impacto clínico sea significativo.

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Introduction

Treatment of differentiated thyroid carcinoma (DTC) rests upon three successive mainstays. The first of these is thyroidectomy, aimed at achieving the most complete possible resection of the unifocal or multifocal tumor and adenopathies that may eventually be affected[1-3]. A second step, one which is indicated in most cases[2-4]. is postoperative ablation of any remaining thyroid and neoplastic tissue by the administration of radioiodine (131I), Finally, most patients are also treated with suppressive doses of levothyroxine (LT4), which is able to inhibit TSH secretion by the pituitary gland over a long time period[2,3,5]. The term "suppressive" therapy does not appear to be adequate in this setting. To suppress means to hold back or abolish, while to inhibit would be more adequate in its medical meaning of transiently suspending a body function or activity through the action of an adequate stimulus (http://www.rae.es/rae.html).

However, because of its wide acceptance in the literature, both terms are used interchangeably in this review.

TSH-suppressive therapy (ST) with LT4 has two goals. One of these is hormone replacement, indispensable in patients who become athyreotic after surgery. The other goal is inhibition of TSH secretion, stimulating thyroid cells. This second effect has been widely accepted in the history of treatment of DTC. However, TSH-suppressive therapy is currently controversial because of the excellent curative prognosis of low-risk DTC and the eventual harmful effects of the subclinical thyrotoxicosis state to which patients are subject over a long period of time[6].

Rationale for TSH inhibitory therapy in DTC

The use of thyroid hormones in patients with DTC is based on both clinical and experimental evidence. The first references to the effect of ST on tumor growth in clinical studies dates back to the 1930s, when tumor regression was reported in two patients with papillary carcinoma after administration of thyroid extracts[7].

TSH was subsequently seen to have a stimulating effect on neoplastic cells[8,9], and cases showing the benefits of LT4 administration in limiting tumor growth were reported[10]. Clinical evidence supporting the use of LT4 as part of the treatment for DTC was mainly obtained from two retrospective studies[11,12] and one prospective study[13]. In the first of these studies[11], after 30 years of follow-up, patients who had received LT4 experienced 25% less recurrence and 50% less cancer-related mortality than those who had TSH levels suggesting hypothyroidism. In the Pujol et al study[12], long-term maintenance of TSH levels lower than 0.1 mU/L significantly improved the disease-free period independently of all other factors. Finally, Cooper et al[13] found that the degree of TSH inhibition was an independent factor for progression in high-risk, but not in low-risk patients.

Experimental studies are based on the effect of TSH on neoplastic cells and have been conducted both in vitro and in experimental animals. Thus, prevention of the occurrence of thyroid tumors induced by goiterogens in rats in which TSH secretion was suppressed giving oral LT4 or by hypophysectomy was reported[14]. Detection of functional receptors for TSH in DTC[15] and observation of activation of the cAMP by TSH in thyroid cells in culture inducing their growth[16] provided evidence for the potential of TSH-suppressive therapy in the treatment of DTC. There are also experimental data which suggest that TSH has an effect of on cell differentiation. Thus, DTC metastases retain some biological functions, such as iodine uptake and thyroglobulin secretion[17] (but usually not hormone secretion), which are dependent on TSH, and may also express the Na+/I+[18] symporter. This, combined with the observation that thyroglobulin levels depend on TSH in patients with DTC metastases, suggests that thyrotropin is able to stimulate functional capacity and, thus, the growth of DTC cells.

However, some questions have recently been raised in this regard. There are functions of thyroid cells which do not depend on TSH[6], and there is evidence of the implication of growth factors[19] and activated oncogenes such as RET/PTC, BRAF, and the RAS family in tumor development[20,21]. The toxic or "hot" thyroid nodule is a clinical model of thyroid cell growth independent of TSH which suggests the permanent activation of a mitogenic cascade not controlled by TSH[6].

TSH inhibitory treatment: indications, target TSH levels, and doses used

The continued wideapread use of ST is currently controversial as the result of our increased understanding of the course of DTC and the possibility of an early cure for low-risk patients. Table 1 summarizes the cases in which the main current guidelines[2,3] for treatment of DTC recommend that ST should be administered and also the target TSH levels. There is general agreement that TSH should be inhibited indefinitely in patients with persistent or recurrent disease, and for periods ranging from 3 and 10 years in high-risk patients. This means that approximately between a third and a fifth of patients with DTC may receive ST for long periods of their lives. It should be noted in this regard that the maintenance of TSH at levels lower than 0.5 mU/L does not additionally decrease thyroglobulin or limit therapy tumor growth[22].

As regards the daily dose of LT4, this should be the lowest required to achieve the desired TSH levels. Doses will usually range from 2.2 and 2.7 µg/kg/day in adults, and may be higher in children (up to 4 µg/kg/day). These doses may have to be reduced by up to a half in elderly patients[23]. A point of interest in this regard is consideration of ST as a situation of "true" subclinical thyrotoxicosis. There is no clear-cut distinction between subclinical and clinical hyperthyroidism and it may depend on the hormonal feed-back reset of each individual[24,25]. For this reason, the monitoring of peripheral hormones, particularly T3, is important to ensure tissue euthyroidism.

Potential harmful effects of TSH inhibitory treatment

There is ongoing scientific debate concerning the possibility that ST has untoward effects on various organs

Table 1 European and American management guidelines concerning TSH-suppressive therapy for differentiated thyroid carcinoma

European Thyroid Cancer Taskforce (2006)[2]
- Mandatory in patients with evidence of persistent or recurrent disease (including detectable thyroglobulin).
- In high-risk patients who have achieved apparent remission, it is advised for 3 to 5 years.
- In low-risk patients, once cure is confirmed, dosage should be decreased until TSH levels are within normal limits (from 0.5 to 1.0 mU/L) are achieved.
- Patients considered to be in complete remission at any time during follow-up should be switched to replacement doses.

American Thyroid Association Taskforce (2009)[3]
- In patients with persistent disease, TSH should be kept at levels lower than 0.1 mU/L for an indefinite time in the absence of specific contraindications.
- In patients clinically and biochemically free of disease but at a high risk, maintenance of ST to achieve TSH levels ranging from 0.1 and 0.5 mU/L for 5 to 10 years should be considered.
- In disease-free patients, particularly those at a low risk, serum TSH levels should be kept in the low normal range (0.3-2 mU/L).
- In patients who have not received ^{131}I, are clinically free of disease, and have undetectable thyroglobulin on ST and a normal ultrasound, serum TSH levels should be kept in the low normal range (0.3-2 mU/L).

or systems[6,27]. A large number of studies and meta-analyses have been published on the potential effects of treatment with LT4 at suppressive doses on the cardiovascular system[28,29], bone mineral density (BMD)[30-33], the central[34-36] and autonomic[37] nervous systems, immunity[38] and hemostasis[39]. The results reported have been conflicting[40]. The reasons for such discrepancies are multiple and greatly depend on various factors such as the size and heterogeneity of the selected sample, patient age, the possibility of undetected clinical or overt hyperthyroidism, the duration and intensity of TSH inhibition, the achievement or not of effective and persistent TSH inhibition, free T4 or T3 levels in blood, the absence of factors associated with the effect to be studied, and the methods utilised to measure the analyzed effects. Studies conducted in patients with endogenous subclinical hyperthyroidism, which are not necessarily extrapolable to the subclinical thyrotoxicosis status characteristic of ST, should also be differentiated[41].

The current state of knowledge concerning the potential effects of ST on different organs or systems is discussed below.

Cardiovascular system

Thyroid hormones have very important physiological effects on the heart and blood vessels[28,42], and the cardiovascular system is highly sensitive to thyroid dysfunction. Since the initial observation by Parry[43], a wide spectrum of cardiac changes related to clinical hyperthyroidism have been reported[44]. These may include short-term effects due to electrophysiological changes induced by thyroid hormones, such as sinusal tachycardia, supraventricular extrasystole, atrial fibrillation, and ventricular arrhythmia; and long-term effects resulting from the increased cardiac load and left ventricular mass leading to diastolic dysfunction, systolic dysfunction at rest or on effort, and structural myocardial changes[26]. Clinical studies analyzing the potential harmful effects of ST on the heart have reached no definitive conclusions. As regards resting heart rate, four studies verified TSH inhibition to values less than 0.05 mU/L, using ECG-Holter methods[45-47] or ambulatory monitoring[48] to assess heart rate, and compared patients with a control group. An increased heart rate was seen in two of the studies[45,46], while no differences were found in the other two[47,48]. As regards structural myocardial changes, there is evidence of an increased left ventricular mass in subclinical thyrotoxicosis[47-52], but some discrepant findings have been reported[53]. Two studies found changes in ventricular function with exercise[46,49], and diastolic function was altered in four[26] out of five studies in which Doppler echocardiography was used. No evidence of the occurrence of ventricular arrhythmia has been found in clinical studies[45,47], but a relationship has been observed between exogenous subclinical thyrotoxicosis and supraventricular arrhythmia[45,46]. However, the relevance of these observations for the morbidity and mortality of patients on ST is not so evident, as is shown by data collected from epidemiological and follow-up studies. Although an association between endogenous subclinical hyperthyroidism and cardiac arrhythmia induced by atrial fibrillation has been found in people over 60 years of age[54-56], its relationship to mortality is controversial. A single study found a five-year relative risk of 2.0 in patients with TSH levels less than 0.5 mU/L[57], but more recent studies[56,58-60] and meta-analyses[61] have not confirmed such an association. With regard to subclinical thyrotoxicosis induced by ST, patients with TSH levels less than 0.03 mU/L have been reported to have an increased cardiovascular risk[62]. However, peripheral hormones were not measured in this study, and overt hyperthyroidism cannot therefore be ruled out. By contrast, other authors did not find this association[63].

In follow-up reports of a series of patients with DTC, specific cardiovascular morbidity and mortality was

approximately 18%-20%, a similar proportion to that seen in a general population of similar characteristics[64,65].

The scientific evidence reported in the guidelines for the diagnosis and management of subclinical thyroid dysfunction published in 2004[41], including a specific section on exogenous subclinical hyperthyroidism, only showed an association between cardiac arrhythmia from atrial fibrillation and TSH levels less than 0.4 mU/L, while associations with all other cardiac parameters were insufficient or weak. Based on this and because of increased life expectancy in developed countries, it has recently been suggested that elderly patients should be considered as being at risk of experiencing arrhythmia with ST[66].

New fields of research into the effects of ST on the heart, such as the assessment of biochemical markers of cardiac dysfunction, have been opened[67].

Skeletal system

Since the description by von Recklinghausen of severe bone involvement in a female patient dying from severe hyperthyroidism[68], great advances have been made in our understanding of the effects of thyroid hormones on bone, ranging from clinical and analytical data[30] to the description of the molecular actions of thyroid hormones[69]. Both growth cartilage and cells involved in bone remodeling (osteoclasts and osteoblasts) express functional thyroid hormone receptors (TRα and TRβ), and T3 therefore exerts direct or indirect actions (due to the production of cytokines and growth or proangiogenic factors) on bone development and bone mass maintenance[30]. On the other hand, a direct effect of TSH as a negative regulator of bone turnover has been reported[70].

A decrease in the intestinal absorption of calcium and phosphate, an increase in calcium excretion in feces and through the skin[71], a shortened duration of bone remodeling, and a negative balance between bone resorption and formation (10% per cycle)[72] have all been found in hyperthyroidism. The final result is a decrease in bone mineral density (BMD)[73] and an increase in the risk of fracture[74,75], which may be reversible with normalization of thyroid function[76]. These effects are more marked in cortical than in trabecular bone.

The potential effect of chronic TSH inhibition with levothyroxine in patients with DTC has been analyzed in cross-sectional[31,32,76-83] and longitudinal[84-87] studies with diverse and sometimes conflicting results. The existence of other factors having a potential influence on BMD, patient age, LT4 doses prescribed, treatment duration, and different bone mass quantification procedures or asymptomatic fractures introduce not only a great heterogeneity, but also confounding factors into the results obtained in most studies. It should be noted that, except in more recent studies[31,32], either a very small number of patients were recruited (2 to 9 in some cases)[78,79,82,84,87,88], no control group was used[76,80,86], or TSH was not inhibited in all patients[76,78,82-85]. Among the few adequately designed studies[31,32,69,86] in which overt hyperthyroidism was ruled out during follow-up by serial measurement of peripheral thyroid hormones[31,32], a 12%-18% decrease in lumbar and femoral BMD was seen in post-menopausal women in one of them[86], but no BMD

reductions were found in pre- and post-menopausal women or in men in the other three studies[31,32,77]. Two meta-analyses[89,90] suggesting an effect on BMD in women are available, but were published some years ago and do not therefore include many studies on the subject. A systematic review[91] concluded that only in post-menopausal women could there be some uncertainty about the possibility that ST affects BMD. The most recent negative studies were again not included in this review.

As regards the risk of fracture, post-menopausal women treated with LT4 showing TSH levels lower than 0.1 mU/L have been reported to have a 2 to 4-fold greater risk of osteoporotic fracture as compared to the general population[62,92]. By contrast, other authors, including ourselves, have not found any such association in either women[93,94] or men[32].

According to data concerning the management of subclinical thyroid dysfunction published by an expert panel based on scientific evidence[41], the evidence for an association between subclinical thyrotoxicosis and BMD decrease or risk of fracture is negative or insufficient, and is only considered as weak in post-menopausal women or women with a prior history of hyperthyroidism.

Systemic symptoms, quality of life

By definition, subclinical hyperthyroidism causes no symptoms. However, the current concept of health includes, in addition to absence of disease (i.e. of symptoms), complete physical, mental, and social well-being. This is why, with advances in medicine, ever increasing importance is now being given to aspects difficult to quantify such as quality of life, a concept mainly based on subjective patient perception. In addition, the significant increase in life expectancy in developed countries has significantly increased the proportion of elderly patients. This age group is particularly susceptible to the potential comorbidities induced by different treatments such as ST with LT4.

A greater incidence of general symptoms of hypothyroidism (palpitations, tremor) has been reported in patients with subclinical hyperthyroidism[47], but an individual sensitivity has been suggested. Contradictory results have been found in anxiety scores, with some studies finding higher scores in patients with subclinical hyperthyroidism[95] while others found no differences[96]. Discrepancies are also marked when a potential decrease in health-related quality of life is analyzed. While some authors found more negative replies in health-related quality of life questionnaires[97,98], such differences were not seen in other long-term follow-up studies of patients with DTC on ST[36].

Central nervous system

The relationship between ST and cognitive impairment or dementia due to Alzheimer's disease has also been analyzed. Two studies are of special interest because of the number of patients recruited[34,35], and their results are again contradictory. The Rotterdam study[35], conducted on 1,846 patients, reported a three-fold greater incidence of dementia and Alzheimer's disease when TSH levels were less than 0.4 mU/L and in association with the presence of

antithyroid antibodies. By contrast, the second study[34], conducted on 829 consecutive patients, found no relationship between Alzheimer disease and TSH levels. It is therefore difficult to draw meaningful conclusions about the eventual relationship between TSH and cognitive impairment. There were confounding factors such as the presence of autoimmunity or depression, and decreased TSH levels could have been either the cause or the consequence of dementia. In fact, guidelines based on scientific evidence[41] consider the connection between neuropsychiatric symptoms and subclinical hyperthyroidism to be either negative or insufficient.

Hemostatic system

European guidelines for DTC management[2] suggest the possibility that ST affects coagulation, establishing a prothrombotic state. However, the article cited in this regard[38] reported only a single study conducted on a very small number of patients whose median free T4 levels were within the limits of overt hyperthyroidism and which did not report free or total T3 levels. Thus, it cannot be stated that all patients had subclinical thyrotoxicosis. In fact, a subsequent systematic review[99] of six middle ranking studies, only reported increases in fibrinogen and von Willebrand clotting factor, of doubtful clinical effect.

Other organs and systems

There are isolated studies reporting potential harmful effects of ST on immune response[100] or the autonomic nervous system[37].

Discussion

It appears evident that the safety of ST has been widely investigated. It is also clear that there is no agreement as to the risk associated with ST, although the most recent, higher quality studies suggest that it is not clinically significant[31,32,64,65]. It is however interesting to be aware of the perception of clinical endocrinologists responsible for the follow-up of patients with DTC. In this regard, in a survey conducted in Spain[101] we asked almost 100 hundred specialists for their opinion as to the potential effects of ST on a series of 14 organs or systems and the clinical relevance of such effects. Widely different opinions were recorded, and no particular option in any item was marked by more than 80% of the specialists surveyed. Among the potential side effects of ST, most physicians surveyed thought that dementia and Alzheimer's disease, decrease in the quality of life, decreased BMD in pre-menopausal women and in men, thromboembolic disease, signs and symptoms of hyperthyroidism, and increased risk of fracture were unrelated to ST, while a majority considered that increased heart rate and decreased bone mineral density in post-menopausal women were related to ST. However, the most outstanding fact was undoubtedly that 80% of physicians surveyed thought that the effects were not clinically significant. It may be inferred from these results that the potential undesirable effects of ST do not condition its use in standard clinical practice.

The concept of ST has changed in recent years because of the excellent prognosis of DTC due to the greater prevalence of papillary carcinoma[102] and the increased sensitivity of TSH measurements, which allows for the fine tuning of LT4 doses[103]. Nevertheless, approximately 20% of patients with high-risk, relapsing, persistent, or progressing tumors may benefit from the effect of ST on tumor growth[104]. One of the key aspects of ST is intensity of TSH inhibition. In young patients, there should be no reason for concern if total and free T3 levels are maintained within normal limits. The most adequate regimen for elderly patients with high-risk DTC, residual tumor, and severe comorbidities (cardiovascular, diabetes mellitus, or osteoporosis) has not yet been clearly defined. These patients have the greatest risk of both cancer progression and eventual adverse effects of ST. The risks/benefits of subclinical thyrotoxicosis should be assessed in these cases[66]. In this regard, patient stratification schemes based on the risk of DTC progression in relation to the potential risk of ST based mainly on patient age and associated comorbidities have recently been proposed[105] (Table 2).

In the future, TSH inhibition may be achieved with thyroid hormone analogues effective on the pituitary gland and with a minimal effect on other organs or systems, as occurs with selective estrogen receptor modulators[106], or by developing retinoids or other compounds which specifically decrease TSH secretion[107]. Research on genetic, biochemical, or morphological markers in high-risk patients may also contribute towards identifying those who could benefit from ST and those who do not require it.

Table 2 Proposed stratification of TSH goals based on the risk of the relapse or progression of thyroid cancer and the risk of eventual complications of subclinical thyrotoxicosis due to TSH inhibitory therapy

	Risk from differentiated thyroid cancer	
	High	Low
Potential risk of TSH suppression		
Low	TSH 0.1-0.5 mU/l	TSH 0.5-2 mU/l
High	TSH < 0.1 mU/l (undetectable?)	TSH 0.5-2 mU/l

(Taken from reference 109).

Conclusions

Patients with thyroid cancer should be treated with LT4 during their lifetimes and should be monitored to prevent adverse effects. In patients with DTC, long-term inhibition of TSH is only required when there is evidence of persistent or recurrent disease. In such cases, overt thyrotoxicosis should be avoided, and LT4 should be given at the lowest doses compatible with achieving the goals of TSH inhibition. The possibility that ST may cause untoward extrathyroid effects continues to be a controversial issue, particularly in elderly patients. Scientific advances will undoubtedly contribute to a better understanding of the eventual side effects of suppressive therapy[108]. Although changes in various organs and systems have been reported, their actual clinical relevance should not be a reason for concern provided normal levels of circulating active hormone are maintained.

Conflict of interest

The authors state that they have no conflict of interest.

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