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Management of Subclinical Hypothyroidism: The Thyroidologists' View

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Key Words
Subclinical hypothyroidism · Dyslipidaemia · Thyrotropin · Hashimoto's thyroiditis

Abstract
Subclinical hypothyroidism is a common finding when serum thyrotropin and thyroid hormones are measured, but the benefits of treating such patients with levothyroxine remain unproven. During the 14th International Thyroid Congress, a debate and discussion relating to three different clinical case scenarios of subclinical hypothyroidism was held. The audience consisted predominantly of members of the European Thyroid Association. Participants (n = 380) voted using an electronic system to express their opinion about the treatment of the 3 cases. For a 53-year-old woman with fatigue and difficulty losing weight, who has a serum TSH of 6.8 mU/l, 49% would treat with levothyroxine. Whereas, for an 84-year-old woman with a serum TSH of 6.8 mU/l, only 8% of participants would treat with levothyroxine. In contrast, for a 39-year-old woman who is trying to become pregnant, with a serum TSH of 4.5 mU/l and strongly positive thyroid peroxidase antibodies, 95% of respondents would treat with levothyroxine. This article details the clinical case scenarios and the results of the thyroidologists' opinions on treatment. It forms a snapshot of the range of accepted clinical practice in this common condition.

Introduction

Subclinical hypothyroidism (SCH) is defined by an elevation of the serum TSH with circulating free thyroid hormone concentrations that are within the reference range [1]. It is a common issue in clinical practice that predominantly affects women, with a population prevalence of between 2 and 10%, which increases in an age-related fashion [2, 3]. More than three-quarters of individuals with SCH have serum TSH concentrations between 5 and 10 mU/l. Although treatment of the mild thyroid failure of SCH with levothyroxine would seem to be a logical approach to management, only a minority of individuals with SCH have symptoms that are typical of hypothyroidism [4–6]. Furthermore, there is scant evidence that symptoms of hypothyroidism, or health-related quality of life, improve following levothyroxine treatment of SCH [7–10].

Another reason to consider treatment of SCH with levothyroxine might be to improve the prognosis of the condition, and several population-based epidemiological studies have shown an association of SCH with ischaemic heart disease, other vascular diseases and cardiovascular mortality [11–14]. Recent meta-analyses confirm the increased risk of vascular disease in individuals with SCH [15], although this risk may be most significant on those who develop SCH at a younger age [16], or in those with

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Table 1. Reasons not to treat SCH

– Serum TSH is not the perfect marker of thyroid hormone action because of its dependence on hypothalamic TRH, on the type 2 deiodinase, on the influence of steroids, cytokines, adipokines and neuromediators (e.g. L-dopa)
– TSH level is not a fixed and immutable parameter: it varies according to diurnal, circannual, some physiological and non-thyroidal factors
– Normal values of TSH are imperfectly defined for every population: the upper limit is age- and race-related, also depending on occult autoimmune thyroiditis, inactivating polymorphisms of TSH receptor, and others
– Only few patients with SCH will progress to overt hypothyroidism
– There is no clear evidence that patients with SCH really suffer any distinct symptoms or have a worse prognosis
– There is no clear evidence that therapy with levothyroxine improves symptoms and prognosis of patients with SCH
– Obesity is a frequent circumstance where high levels of TSH are discovered, but lack of thyroid hormone is not generally the culprit
– Higher risk of infertility, miscarriages, preterm delivery and impairment of neuropsychological development of the fetus have been suggested to result from SCH during pregnancy. However, studies may be confounded by differences in iodine intake, associated autoimmune disorders, older age of parturient women
– Therapy with levothyroxine is not free of inconvenience and risks
– Extreme longevity is associated with increased serum thyrotropin

Table 2. Treatment indications for SCH

Treat at all ages if:
– TSH >10.0 mU/l
– Pregnancy (or pre-pregnancy)
Consider treatment, if:
– Age <65 years
– Symptoms or signs of hypothyroidism
– High vascular risk including
Ischaemic heart disease
Diabetes
Dyslipidaemia
Cigarette use
– Positive thyroid peroxidase antibodies
– Goitre

the highest serum TSH concentrations (>10.0 mU/l) [17]. However, there are no studies that support an improvement in 'hard' clinical outcomes of vascular disease such as a reduction in clinical events or improved mortality following treatment of SCH with levothyroxine. Instead, several studies suggest a modest reduction in serum cholesterol concentrations [18, 19] and improvement in certain markers of vascular disease or endothelial function [10, 20–22], which may be surrogate indicators for a clinical benefit.

Therefore, while levothyroxine seems like a reasonable treatment option for many patients with SCH, the evidence for benefit, either in terms of symptom or outcome improvement, is marginal. Thus, learned clinical practice guidelines from several authoritative societies do not endorse widespread treatment of SCH patients with levothyroxine [23–25], particularly in individuals with serum TSH in the 5.0–10.0 mU/l range, who constitute the majority of SCH patients. This instinct towards conservative management is encouraged by the findings of several large studies that show that 40% or more of individuals who are prescribed levothyroxine have serum TSH values that are outside the reference range [4, 26], with both overtreatment and under-replacement being common. So, levothyroxine has the potential to be a detrimental treatment, exposing the SCH patient to excess circulating thyroid hormone concentration with a concomitant concern over skeletal integrity and tachyarrhythmic complications [27, 28]. Nevertheless, physicians are faced with making a decision about treating an individual patient, not generally a population, and substantial numbers of people with SCH do receive treatment with levothyroxine, against the prevailing learned opinion.

In order to explore the factors that clinicians take into account in making a decision about treatment of SCH, a debate on this subject was held during the 14th International Thyroid Congress (Paris, September 13, 2010). This event took the form of two short set-piece lectures delivered by experienced clinical thyroidologists (M.V. and J-L.W.), each taking opposing views as to the need for levothyroxine treatment of SCH. The salient points of these lectures are summarized in tables 1 and 2. The experts then answered questions and gave viewpoints on three clinical case scenarios and the audience had an opportunity to give their opinion about management of each case, using an electronic voting system. This article summarizes the opinions and collective expertise of a large audience of clinical thyroidologists in management of SCH patients.

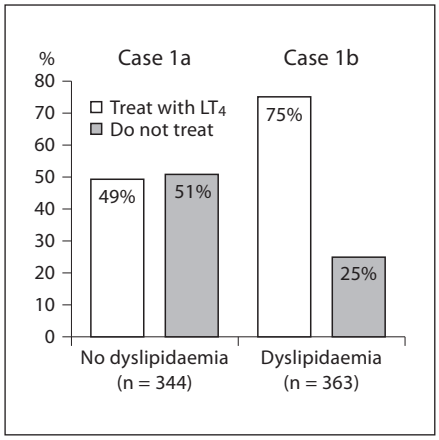

Fig. 1. Case scenario 1, 53-year-old female, TSH 6.8 mU/l.

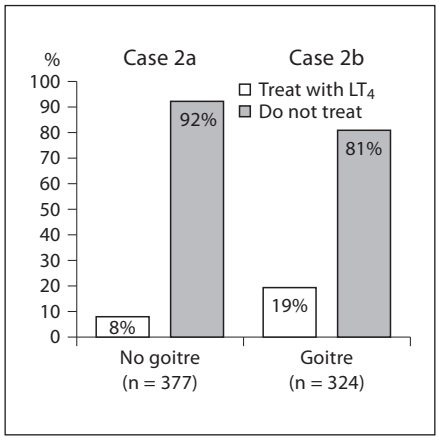

Fig. 2. Case scenario 2, 84-year-old female, TSH 6.8 mU/l.

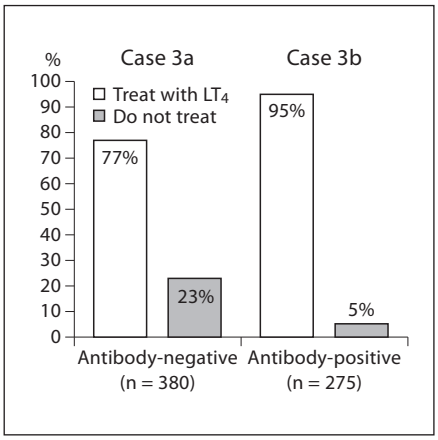

Fig. 3. Case scenario 3, 39-year-old female, TSH 4.5 mU/l.

Participants and Methods

Three hundred and eighty individuals responded to one or more of the six questions in the clinical case scenarios by using a digital handset. For each scenario the case was presented, discussed and the participants were then asked to vote. In each case, the choice was 'treat with levothyroxine (LT_4)' or 'do not treat'. The audience was derived primarily from the membership of the American Thyroid Association, the Asia and Oceania Thyroid Association, the European Thyroid Association and Latin American Thyroid Associations. By geographic origin, 60% of the participants were from Europe, 12% from Latin America, 11% from North America (grouped as Americas), 11% from Asia, with 4 and 2% from Australia and Africa (grouped as Others), respectively. The majority of participants identified themselves as being engaged in 'Academic' (Hospital or University) practice (78%), whereas 22% identified themselves as being in 'Private' practice.

Case Scenarios and Results of Participant Opinion

Case 1a: A 53-year-old businesswoman has had difficulty losing weight for the last 2 years. She complains of feeling physically exhausted and of being mentally unfocussed. She has been taking combined oestrogen/progesterone hormone replacement therapy since her menopause. Her serum TSH is 6.8 mU/l, with normal circulating free thyroxine concentration. The results of the participants' opinion are shown in figure 1.

Case 1b: As in case 1a, but she was also now noted to have dyslipidaemia, with a serum LDL cholesterol of 6.5 mmol/l (251 mg/dl) and HDL cholesterol of 1.1 mmol/l (43 mg/dl).

Case 2a: An 84-year-old woman complains of feeling generally tired and less energetic than previously. Her son is concerned that she falls asleep every afternoon. Five years ago she had a myocardial infarction, but has no current angina. Her serum TSH is 6.8 mU/l, with normal circulating free thyroxine concentration. The results of the participants' opinion are shown in figure 2.

Case 2b: As in case 2a, but examination reveals a moderate symmetrical smooth goitre, estimated to be about 30 g in weight by palpation.

Case 3a: A 39-year-old woman is trying to become pregnant following a recent miscarriage at 11 weeks' gestation. She feels well in herself. Her serum TSH is 4.5 mU/l, with normal circulating free thyroxine concentration. Serum thyroid peroxidase antibodies were negative. The results of the participants' opinion are shown in figure 3.

Case 3b: As in case 3a, but thyroid peroxidase antibodies are strongly positive (>1,300 IU/ml).

After these specific case scenarios, participants were asked to agree or disagree with the general statement 'do not treat subclinical hypothyroidism' (fig. 4). Answers to this question are also shown with participants identified by their stated role in academic/hospital practice versus private practice, and by geographic region of origin, including Europe, North and South America (Americas) and Asia, Africa and Australia (Others).

Discussion

The indications for the treatment of SCH with levothyroxine remain poorly defined [29], particularly in the patient group with serum TSH in the 5.0–10.0 mU/l range. The three clinical case scenarios discussed during this presentation were chosen to probe the factors that thyroidologists consider important in deciding about treatment of mild SCH. There are several findings worthy of comment. Firstly, it is interesting to note that the thyroidologists were more likely to recommend treatment with levothyroxine for the younger patient, with 77, 49 and 5% endorsing treatment of patients aged 39, 53 and 84 years. However, in case scenario 3 the fertility issue may have had greater weight than the young age. Nevertheless, the current finding that older individuals are less likely to be treated is in contrast to the previous postal

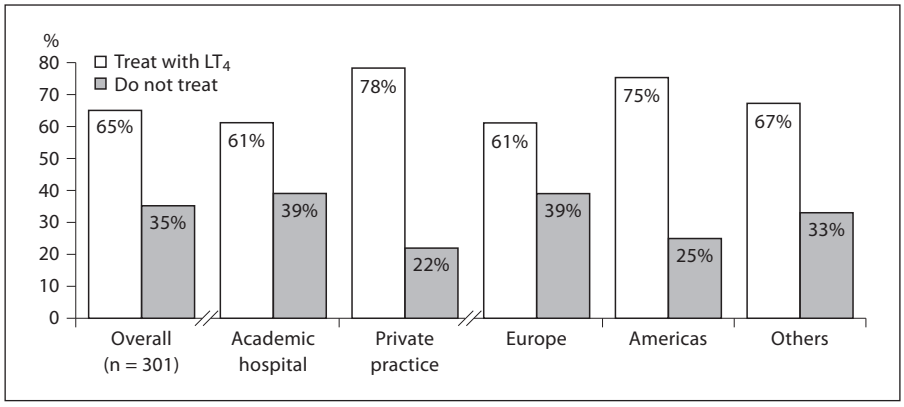

Fig. 4. In general, how do you manage subclinical hypothyroidism?

survey of members of the American Thyroid Association that was published in 2001 [30]. In that study, both the hypothetical patients had a higher reported TSH of 8.2 mU/l and positive autoantibodies, with 96 and 92% of respondents endorsing treatment at the ages of 27 and 71, respectively [30]. This difference may reflect the clinical practice of the predominantly European thyroidologists in this current survey, or the impact of some more recently reported information that there is an increase in the serum TSH reference range amongst healthy older people [31]. This is supported by the findings of an upper limit of TSH of 7.5 mU/l being found in a study of over 80-year-olds [32]. In addition, several studies now show that SCH is not associated with adverse patient outcomes in advanced old age [33, 34].

As explored by case scenarios 1 and 2, the presence of both dyslipidaemia and goitre influenced the participants towards treating SCH in these cases. The proportion of participants recommending levothyroxine treatment increased from 49 to 75% (fig. 1) when dyslipidaemia was present; the largest change of opinion observed out of any of the factors that we explored. This is a little surprising as the available data suggests a very modest reduction in LDL cholesterol, in the order of 0.2 mmol/l, is to be expected from treating SCH with levothyroxine [18]. Thus, levothyroxine is not an effective therapy for correcting dyslipidaemia for most SCH patients. The presence of goitre in case scenario 2 increased the preference to treat the elderly patient with levothyroxine from 8 to 19% (fig. 2). Goitre provides evidence for the physician that there is definitely an intrinsic thyroid disease and thus appears to lower the threshold for treatment. Indeed, high TSH in this scenario may be considered as a trophic factor for thyroid growth, and levothyroxine therapy may therefore have a role in goitre reduction. Despite these considerations, there is no evidence base to support a better outcome from treatment of SCH in the presence of goitre. Nevertheless, the opinions of the participants are certainly in accord with those of a high profile review, which has suggested that SCH individuals with either dyslipidaemia or goitre are treated [35].

Over recent years, evidence has accumulated that both minor perturbations in thyroid function, and the presence of thyroid autoantibodies even with normal thyroid function, may be associated with adverse obstetric outcomes. For instance, several studies show an increased rate of early pregnancy loss in those with higher first trimester TSH values [36–38]. A randomized trial of levothyroxine treatment in euthyroid, but thyroid peroxidase antibody-positive individuals has shown a reduction in pregnancy loss with levothyroxine treatment [39]. Case scenario 3 probed how widely the findings of these studies have influenced current practice. Figure 3 demonstrates that 95% of participants would treat a woman seeking pregnancy with positive thyroid peroxidase antibodies and a serum TSH of 4.5 mU/l, following a single miscarriage. Thus, it is clear that almost all expert thyroidologists take this issue seriously, have accepted the research findings and have rapidly translated them into their clinical practice.

The results of this survey may differ from the previous study for several reasons. Our participants consisted predominantly of thyroidologists practicing in Europe (60%) compared to the previous survey, which involved members of the American Thyroid Association. Figure 4 contains data that suggest there are variations in practice between Europe and other continents, as well as between hospital-based and private practitioners. Our participants were also part of a live audience, with brief expert analysis of each cases scenario being made prior to them

expressing their opinions. Thus, the nature of the event may have influenced practitioners' views about the cases. Much new research information has also been reported in the 9 years since the postal survey was performed, and real-life clinical practice is likely to have changed as a result. This survey is also limited in that a relatively scant clinical scenario was given, and that with a real patient much more detailed information would be obtained, importantly including the actual values of the free thyroid hormone measurements. Nevertheless, the survey does broadly represent the opinions of a large group of practicing thyroidologists and thus has utility despite the above cautions.

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