Recent evidence sets therapeutic targets for levothyroxine-treated patients with primary hypothyroidism based on risk of death

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Abstract

Since the introduction of sensitive assays for serum thyroid-stimulating hormone (TSH) clinicians have advised hypothyroid patients to adjust the dose of levothyroxine (L-T4) in order to achieve a normal serum TSH. A minority of patients are dissatisfied with this treatment strategy and experience symptoms. Some indirect evidence suggests that a normal serum TSH may not necessarily reflect euthyroidism at the tissue level in patients treated with L-T4. Increasingly hypothyroid patients demand higher doses of L-T4 or liothyronine (L-T3) or animal thyroid extract, often purchased online, and titrate the dose against symptoms, although ample evidence suggests that combination treatment (L-T4 with L-T3) is no more effective than L-T4 alone. Community surveys show that up to 53% of treated hypothyroid patients at any time have a serum TSH outside the normal range. The recommendation by guidelines that the upper limit of the normal range for serum TSH should not be exceeded is supported by robust evidence and is generally accepted by clinicians and patients. However, until recently the lower limit of serum TSH for optimal L-T4 replacement has been controversial. New evidence obtained by two independent large population studies over the past two years has shown that mortality of hypothyroid patients treated with levothyroxine is increased when the serum TSH exceeds or is reduced outside the normal reference range. It is estimated that the implementation of a policy of normalising serum TSH in hypothyroid patients will reduce the risk of death of 28.3 million people in the USA and Europe alone.

European Journal of Endocrinology
(2021) **184**, C1–C3

European Journal of Endocrinology

Introduction

Many hypothyroid patients use the internet as a major source of information about their diagnosis (1, 2). They soon become aware that there are heated controversies and an apparent divide between some patient groups and endocrinologists. These are centred around diagnosis, therapies and treatment targets. Conventional endocrine practice is challenged by a vocal minority of patients and some 'experts' who purport that the diagnosis should be made based on symptoms and a thermometer, that levothyroxine (L-T4) is generally ineffective or should be combined with liothyronine (L-T3), or substituted with animal thyroid extract. Various supplements, diets and alternative treatments are also promoted, and patients are advised that the therapeutic target is relief of symptoms, often through self-medication, titrated and varied according to symptoms, if necessary on a daily basis (1, 2). The evidence base for these views is patient testimonies.

Trends in presentation, diagnoses and treatment

Over the past two decades, requests for thyroid function tests have risen and the threshold for commencing

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-20-1229

Published by Bioscientifica Ltd.

thyroid hormone replacement has diminished. A minority (10–15%) of patients are dissatisfied with L-T4 treatment and demands on physicians for combination (L-T4+L-T3) treatment or animal thyroid extract are increasing (3). Paradoxically, a wealth of evidence from randomised controlled trials shows no difference of L-T3 containing treatments compared to L-T4 (4).

Guidelines

The American Thyroid Association (ATA) guidelines on hypothyroidism (5) recommend normalisation of the serum thyrotropin (TSH) concentration. Aiming for a serum TSH less than the upper limit of the normal range is supported by evidence demonstrating increased cardiovascular events and mortality associated with raised TSH (5). With regards to overtreatment with L-T4 the ATA guidelines state 'we recommend avoiding thyroid hormone excess and subnormal serum thyrotropin values, particularly thyrotropin values below 0.1 mIU/L, especially in older persons and postmenopausal women', based on the absence of evidence for morbidity associated with a low yet not completely suppressed TSH, at the time of publication of the guidelines. The ATA guidance about the lower limit of TSH is complex and the message not easy to communicate. A widespread belief among hypothyroid patients is that a low TSH of no consequence, hence self-adjustment of thyroid hormone dose based on symptoms (which often leads to over-replacement) is perceived as being safe (1, 2).

Recent evidence

In the last 2 years, two large studies examined health outcomes of hypothyroid patients treated with L-T4 in relation with TSH levels (6, 7). A Danish study included 2908 hypothyroid patients (6). The median follow-up was 7.2 years and the study investigated mortality, compared to matched euthyroid individuals. There was a 5% increased risk of mortality in treated hypothyroid individuals for every 6 months of raised serum TSH. Patients with low or suppressed TSH, as a result of overtreatment, had an 18% increased risk of mortality for every 6 months of low or suppressed TSH. In the UK study, records from 162 000 patients diagnosed with hypothyroidism from general practices were used. Median follow-up was 6 years (7). Hypothyroid patients whose TSH levels were in the normal range, had no evidence of negative long-term health outcomes. However, increased mortality was observed in both the lowest and highest TSH categories. Unlike previous evidence, these two studies were sufficiently powered to assess mortality as an outcome. Ideally, one would wish to have evidence generated from prospective randomised double-blind studies to confirm these findings. Such research will require a very large sample size, considerable resources, will take several years to complete and will probably be deemed unethical. The current level of knowledge will therefore have to suffice.

Missed opportunity

In the 2019 National Institute for Health and Care Excellence (NICE) guidelines (https://www.ncbi.nlm.nih.gov/books/NBK550900/) for diagnosis and management of patients with thyroid diseases, the two studies that link mortality with serum TSH outside the normal range were not cited (6, 7). The recommendation stated: 'The goal of treatment is to alleviate symptoms and align thyroid function tests within or close to the reference range' (https://www.ncbi.nlm.nih.gov/books/NBK550900/). It seems that an opportunity to highlight the association between a serum TSH outside the normal reference range and risk of death was missed. Unfortunately, rogue blogs and unregulated patient sites continue to preach that a low or suppressed serum TSH is of no relevance, remain unchallenged, and continue to beat the drums of misinformation.

Under- and over-treatment of hypothyroidism poses a significant societal burden

Population surveys have shown that low and high serum TSH among hypothyroid patients treated with L-T4 is common. At any one time, 53% of treated hypothyroid patients have a serum TSH outside the therapeutic target (8). Given that the prevalence of hypothyroidism is about 5%, and that the population of USA and Europe are 330 and 740 million, respectively, there are 16.5 million hypothyroid patients in the USA and 37 million hypothyroid patients in Europe; of these, approximately half (53%) at any one time have a serum TSH outside the normal range. It follows, therefore, that 8.7 million hypothyroid patients in the USA and 19.6 million in Europe (total 28.3 million) are at risk of premature death from under- or over-treatment. The societal burden of this

is considerable and it takes a mere change in dosage of one of the cheapest medications known to mankind to reverse it.

Action is needed

A first step in the right direction is for dissemination of this message to all those who are involved in the care of patients with hypothyroidism: endocrinologists, internists, primary care physicians and above all hypothyroid patients themselves. Professional and patient-led organisations have a responsibility to work towards changing perceptions and optimising the treatment of hypothyroidism. For those patients who have a normal serum TSH, this message will be reassuring. For those who are outside the normal range, one hopes it will provide an incentive to normalise their serum TSH. The studies by Lillevang-Johansen *et al*. (6) and Thayakaran *et al*. (7) do not apply to patients who are on L-T4+L-T3 treatment, T3 alone or animal thyroid extract. While on these L-T3 containing treatments the serum TSH may be normal, nonetheless it is accompanied by wide fluctuations in Free T3 (FT3) levels often exceeding the upper limit of the reference range. In these cases, we have very little information on long-term safety, but there are reasons to be concerned that the highly unnatural fluctuations in FT3 levels, may turn out to be detrimental to health. The value and limitations of serum TSH as a single marker of thyroid status are controversial topics, which the cited studies (6, 7) do not address, however, they provide a useful framework upon which clinical decisions can be based. Numerous factors determine the individual dose requirements for levothyroxine (9) (BMI, concomitant medications, gastrointestinal comorbidities) and physician knowledge of these variables can facilitate reaching therapeutic targets rapidly, and obviate the temptations of patient self-medication and unnecessary searches for alternative diagnoses and levothyroxine formulations.

Conclusion

The time has come to take notice of the significance of serum TSH outside the normal reference range and the implicit risks of mortality in patients treated with thyroid hormones.

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

Funding
This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 27 October 2020
Revised version received 17 November 2020
Accepted 8 December 2020