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Therapeutic challenges in the application of serum thyroid stimulating hormone testing in the management of patients with hypothyroidism on replacement thyroid hormone therapy: a review

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Running header: Practical issues in the management of patients with hypothyroidism

Abstract

Normalising serum thyroid stimulating hormone (TSH) levels by lifelong treatment with levothyroxine (LT4) remains the primary goal of therapy for patients with hypothyroidism. The reference ranges for TSH are derived from populations with (supposedly) normal thyroid function. But, TSH results are affected by a number of factors including alterations in TSH levels with age, concurrent illnesses, circadian rhythm, inter- and intra-assay differences and some commonly-used medications that interfere with thyroid function or the TSH test. Furthermore, some patients are complex to manage and bringing serum TSH to within its reference range does not always resolve their symptoms of hypothyroidism. In others, changes in TSH within the reference range may provoke symptoms in some sensitive patients, and others may have a personal "set point" for thyroid hormone levels that represents normal function for that individual, but which is outside the population reference range. The introduction of updated LT4 formulations, with better dosing accuracy and stability compared with older versions, should, in theory at least, provide better stability and accuracy of dosing over time. However, the new LT4 formulations were associated with manifold increases in the number of self-reported adverse events. Therefore; patients with hypothyroidism as well as the clinicians managing them need to better understand the utility as well as the limitations of the widely-used TSH measurement. In addition, both pharmaceutical companies and the prescribing clinician need to take greater care when patients are switched from older to newer formulations.

Key words: levothyroxine; hypothyroidism; thyroid; thyroid stimulating hormone; narrow therapeutic index drug; new formulation

Introduction

The thyroid gland secretes two principal hormones, triiodothyronine (T3) and thyroxine (T4), formed by deiodination of T3.[1] A synthetic form of T4, levothyroxine (LT4), is the principal treatment for hypothyroidism, and blood levels of TSH serve as the principal biomarker of thyroid function according to current management guidelines in this area.[2] While the majority of patients with hypothyroidism are managed successfully using normalisation of TSH during lifelong treatment with LT4, some are more difficult to manage, with apparent symptoms despite normalisation of TSH, or discordant results for tests of different thyroid hormones. In this review we discuss the status and limitations of TSH testing and consider some practical implications of administering LT4 as a drug with a narrow therapeutic index, as defined by regulators.

Thyroid stimulating hormone is the primary marker for establishing euthyroidism in a hypothyroid patient

Why use TSH as the main biomarker for thyroid function?

According to the guideline for the management of hypothyroidism from the American Thyroid Association (2014), the principal goals of management of hypothyroidism are normalisation of symptoms, signs and to normalise the level of TSH and to avoid over treatment.[2] TSH is essentially an indirect measure of thyroid function: it is secreted from the pituitary gland and acts on the thyroid to increase secretion of thyroid hormones. Abnormal TSH levels are common in the population: in the year 2002, the nationally representative US National Health and Examination Survey III cohort (1988–1994) found that 4.6 of community-dwelling individuals had hypothyroidism (ranging from about 2–14% depending on age and ethnicity).[3]

The principal reason for using serum TSH, and not thyroid hormones *per se*, as the first-line test of thyroid function relates to the non-linear relationship between the levels of free thyroxine (FT4) and TSH. Because of this relationship, a 2-fold alteration in the level of FT4 translates to a 10–100-fold change in the level of TSH.[4] Accordingly, relatively large changes in TSH are more straightforward to measure routinely than relatively small changes in FT4 or free triiodothyronine (FT3).

Hypothalamic/pituitary disorders can also affect thyroid function through abnormally low levels of TSH.[5] These are rare (1 in 80–120,000[5]), and mostly due to tumours, or prior radiation therapy or surgery.[5] Patients with central hypothyroidism may be under dosed with LT4, compared with patients with primary hypothyroidism.[6] A detailed account of their diagnosis and management of

hypothlamaic pituitary disorders is outside the scope of our review, and this has been reviewed elsewhere.[7,8]

In summary, the level of TSH provides an appropriate index of thyroid function for most hypothyroid patients. Bringing the TSH level back to within its reference range is usually the principal means employed by the physician to adjust the dose of LT4 for a patient with hypothyroidism.

Limitations of TSH as a biomarker for thyroid function

The TSH test has some limitations when used as a marker of thyroid status, and may be misleading in some other situations. Inter-patient variations exist in relation to differences between the tests themselves, and in the clinical practices used to manage patients with suspected thyroid disease.[9,10] "Macro TSH", a high molecular weight form of TSH, appears to be recognised variably by the assay methodologies used by commercial laboratories, and may provide another potentially important source of both inter-patient variation and discordance between the reported TSH level and the individual patient's clinical thyroid status.[11]

The test *per se* involves comparison of an individual patient's TSH result with a reference range that has been defined across a population of apparently euthyroid subjects. In the past, the populations used to define "normal" TSH have been contaminated with subjects with unknown thyroid disease, which distorted the upper limit of the reference range.[12,13] The upper limit of reference ranges for TSH has reduced over time, from about 10 mIU/L to about 4–5 mIU/L, a development driven partly by the introduction of more sensitive and accurate TSH assays which can effectively exclude some of these outliers.[12,14,15]

Nevertheless, the reference ranges for thyroid biomarkers are broad in physiological terms, having been defined across populations, while the variation of these markers in individual subjects appears to be much lower.[16] Accordingly, variations in thyroid hormone levels of sufficient size to induce meaningful changes in thyroid function may not exceed the reference ranges.[16,17] Individuals have their own "set points" for the operation of the hypothalamic-pituitary-thyroid axis that differ from the relationships between TSH and FT4 documented in populations.[16,18] This means that, for example, an abnormal FT4 level may persist despite TSH being within the normal range, and a normal FT4 level for one patient may be abnormal for another, so that adjustment of TSH levels using LT4 in an attempt to corral thyroid marker levels within reference ranges may result in appropriate thyroid function for that individual.[19] Levothyroxine therapy appears to shift the position of the set point over time, with a gradual reduction in the dose of LT4 required lower TSH (where elevated) although some of this change is due to ageing (see below).[20]

Other limitations of the TSH test (excluding patients diagnosed with pituitary disorder or pituitary tumours) include unreliable readings due to non-thyroidal illness, recent treatment for thyrotoxicosis, concomitant treatments that interfere with thyroid hormone function or the TSH assay (including lithium, amiodarone, glucocorticoids, non-steroidal anti-inflammatory drugs and others), or disorders of thyroid hormone metabolism.[19,21] Treatment with metformin has also been shown to reduce levels of TSH in euthyroid subjects,[22] suggesting careful attention to thyroid function when starting, stopping or changing the dose of this widely-used antidiabetes agent. Adiposity may also modulate thyroid function: a study in 350 euthyroid subjects with morbid obesity demonstrated higher TSH and lower FT4 in those without anti-thyroid antibodies, compared with euthyroid subjects of normal weight.[23] This study also showed that thyroid autoimmunity was less likely to account for the presence of autoimmunity in obese vs. normal weight subjects matched for TSH levels. The impact of obesity on thyroid status is likely to become more important over time, as the prevalence and severity of obesity continues to increase in many populations.[24] Thyroid hormone levels are subject to circadian and seasonal variations, which may give rise to variability of readings within a single subject.[9] Thyroid hormone status also changes markedly during pregnancy (the thyroid increases in size and thyroid hormone secretion increases by about half at this time[25]) and with age: Fig. 1 shows an example of age-related reference ranges for TSH derived from a large community-dwelling population.[26] The authors of this study speculated that the increase in the upper bound of the reference population with increasing age would be enough to reclassify a substantial (although not quantified) number of elderly patients from hypothyroid to euthyroid if these age-related ranges were used instead of the standard reference range for all ages.

Clinical status of biochemically euthyroid patients

A review of the clinical consequences of variations in thyroid hormones within the reference range concluded that there is evidence for significant association of renal dysfunction, weight gain, metabolic syndrome and other cardiovascular risk factors with higher TSH, and increased risk of osteoporosis and fractures associated with lower TSH.[17] A large, recent meta-analysis of studies reporting thyroid status found that hypothyroid patients with normal TSH had significantly higher LDL-cholesterol and total cholesterol compared with controls without thyroid disease suggesting that normalisation of TSH according to current practice does not necessarily normalise markers of metabolism that are relevant to long-term clinical outcomes.[27] A cross-sectional study from the same authors found that hypothyroid patients on LT4 treatment had higher body mass index, and were more likely to be taking cardiovascular medications (-blockers and statins), compared with controls, despite normalisation of TSH.[28]

The normalisation of symptoms of hypothyroidism by adjustment of TSH levels can be challenging, as these are often vague and nonspecific and develop over time.[29] Indeed, the Colorado Thyroid Disease prevalence study found that more than half of euthyroid subjects reported at least one symptom consistent with thyroid disease, and about one in seven reported at least four such symptoms.[3] Indicators suggestive of hypothyroidism, including dry skin, tiredness, subjectively poor memory/cognition and muscle symptoms, are frequently observed in both people who are euthyroid and in people with elevated TSH.[29] Persistent symptoms of thyroid dysfunction appear to be common in a significant minority of hypothyroid patients managed with LT4.[28,30] Administration of LT4 to patients with symptoms of hypothyroidism, but with thyroid hormones within reference ranges, had no effect relative to placebo on cognitive function and psychological wellbeing.[31] A meta-analysis, in contrast found no benefit for quality of life or thyroid symptoms associated with management of subclinical hypothyroidism with LT4 replacement.[32] Current guidelines from the American Thyroid Association counsel strongly against treatment with LT4 for people with hypothyroid-like symptoms despite normal biochemical indices of thyroid function.[2] Careful evaluation of these patients is also required, to identify possible non-thyroid causes of these symptoms, often with a referral to secondary care.[33]

LT4 is essentially a prodrug for triiodothyronine (T3) and in principle these hormones could be given in combination to a hypothyroid patient. To date, however, administration of LT4 + T3 to patients with hypothyroidism has not provided convincingly superior results to administration of LT4 alone.[34] Debate continues as to what extent inappropriate dosing and other aspects of clinical trial design may have contributed to the disappointing outcome of these trials, and research continues, for example to identify subsets of patients who might benefit from this approach.[34,35] For now, at least, clinical management guidelines and statements from expert societies do not support for addition of triiodothyronine to the regimens of such patients, especially within the primary care setting, as a positive benefit/risk balance for this strategy has yet to be demonstrated adequately.[2,33,36,37]

Accuracy of dosing of levothyroxine

How important are small variations in levothyroxine dosage?

Minor fluctuations in thyroid hormones are often well tolerated by patients with hypothyroidism,[38] but certain groups of patients, for example the elderly (especially where coronary heart disease is present), pregnant women or patients with residual thyroid cancer after treatment may be especially sensitive to small changes in thyroid hormones.[39] An unexplained apparent high level of sensitivity to changes in thyroid hormones may also be present in people without these conditions.[39]

The US Endocrine Society has raised concerns about abrupt changes in doses of LT4 after switching of patients between LT4 preparations, even when these have satisfied formal criteria for bioequivalence with one another, as a result of the high level of sensitivity of the body to thyroid hormone levels.[40] US guidelines recommend re-evaluation of thyroid status following a change of LT4 preparations, although this is acknowledged as a "weak recommendation" based on "low quality evidence".[2]

LT4 has been designated a "narrow therapeutic index" drug by regulatory authorities, on the basis of having "a risk of clinically relevant difference in efficacy or safety between two products even when the conventional criteria for bioequivalence … are met".[41] Accurate dosing is therefore important once the dosage is at or near the long-term maintenance dose. Regulators increasingly require manufacturers of LT4 products to improve their formulations to support more accurate and consistent dosing, in order to minimise fluctuations in health status associated with variations in the actual dosage of LT4, either when switching between products of the same stated dose, or between batches of the same product. Older product standards required the actual delivered dose of LT4 to lie within 90–100% of the stated dosage over the tablets' entire shelf life (typically 3 years); a number of countries have tightened this specification to a range between 90% or 95% and 105%.[42-44] The new product must be bioequivalent with the old product, again to a tighter specification. Specifically, bioequivalence is usually achieved if geometric mean ratios and their 90% confidence intervals for key pharmacokinetic parameters (the area under the plasma concentration-time curve [AUC] and/or the maximal plasma concentration achieved [Cmax]) lie between 80% and 125%; the corresponding range for narrow therapeutic index drugs such as LT4 is 90–111%.[41,45,46] As pharmacokinetic studies are carried out routinely in healthy volunteers, it is possible in principle that bioequivalence findings could differ in populations of patients with medical conditions. We are unaware of clinical evidence of this phenomenon in patients receiving LT4 for hypothyroidism, however.

Experience from the introduction of a new levothyroxine tablet consistent with newer regulatory guidance

The introduction of a new formulation of a widely-prescribed formulation of LT4, developed to be consistent with evolving regulatory guidance in this area,[47,48] provides a useful case study on the practicability of using such an updated preparation in routine patient care. The new and old formulations are formally bioequivalent (under the "narrow therapeutic index drug" criteria, as described above, with full interchangeability between tablet strengths), and the amount of active

LT4 remains within 95–105% of the labelled dose across its shelf life of 3 years, irrespective of the local climate.[47]

Recently published pharmacovigilance reports, based on unsolicited reports of adverse events in France (the first country where the new formulation was launched), have been used to quantify the impact of the new formulation on hypothyroid patients who received the old and/or the new formulations of LT4.[49] Some caution is required regarding the interpretation of this type of real-world evidence, as information is often lacking on the time between switching and appearance of adverse events, TSH levels, medical history and comorbidity, and anonymous reports (accounting for most of the side-effects described in this analysis) cannot be followed up further. The switch from old to new formulations was accompanied by a large (~150-fold) increase in the number of spontaneous reports of adverse events. The proportion reporting new adverse events with the new formulation accounted for about 1.4% of users of this LT4 preparation in France. Slightly more than half of patients had TSH levels in the normal range (where these data were available),[49] which is consistent with real-world data from elsewhere.[3]

Examination of individual side-effects revealed that most were consistent with the symptoms of hypothyroidism, and that no new safety signal had appeared after the switch to the new formulation.[49] A large increase in spontaneous adverse event reporting occurred after the introduction of a different LT4 preparation in New Zealand in 2007–2008, which was also bioequivalent with its previous formulation.[50] In both of these cases, social and broadcast media reporting of initial reports may have fuelled the growth in subsequent reports,[49,50] and influenced the way that patients take the medication, as has been observed previously elsewhere for LT4[50,51] and other drugs.[52]

A dose-for-dose switch between LT4 preparations that are consistent with updated regulatory guidance on establishing bioequivalence should support continuity of thyroid function management without additional thyroid function testing beyond that required for the patient's routine care. The real world data described above show that the vast majority of patients switched between these formulations without new tolerability problems. It is important to recognise that new strategies are needed in the age of social media to handle an increased rate of reporting of adverse events, in a way that allows clear identification of a new safety signal. When, as in this case, regulators require a new formulation to be introduced, patients need to be briefed carefully by their healthcare practitioners on the reason for the change in their medicine, and how the new preparation relates to the old, to support continuity of their care.

Conclusions

Normalising the level of thyroid stimulating hormone remains the primary goal of therapy for patients with hypothyroidism. A number of limitations relating to patient and disease factors apply to the use of TSH as the primary biomarker of thyroid function, however, and reports of patients with hypothyroid-like symptoms, despite within-range TSH, persist in real-world practice. Patients often report changes in wellbeing after small changes in the dosage of LT4. Regulators are driving improvements in formulations of LT4, which provides opportunities for more stable, reproducible dosing, but also requires careful communication with patients and clinical teams to manage the switch.

Transparency

Declaration of funding

This manuscript was sponsored by Merck KGaA.

Declaration of financial/other relationships

UG-H is an employee of Merck KGaA, the pharmaceutical sponsor of the updated LT4 preparation described above. SR has acted as a speaker and member of advisory boards for Merck KGaA. Peer reviewers on this manuscript have received an honorarium from CMRO for their review work but have no other relevant financial relationships to disclose.

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