

The Dilemma of Treating Subclinical Hypothyroidism: Risk that Current Guidelines Do More Harm than Good

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Dear Editor,

The recent European Thyroid Association (ETA) guideline on the treatment of subclinical hypothyroidism (SCH) [1] will potentially be widely used by clinicians faced with this common condition. Although the report includes much useful background and guidance, we suggest that the approach recommended there carries potential risks, with the likely outcome of an increase in the proportion of 'younger' elderly patients treated for SCH and the withholding of thyroxine treatment in the very elderly, in the absence of any good evidence that this will give net clinical gain.

We suggest that the current uncertain state of evidence merits a very simple approach and that watchful waiting with repeat thyroid function tests is the appropriate strategy for most patients with persisting subclinical hypothyroidism. The exception to this are patients with biochemical SCH who have one or more symptoms that cannot be explained otherwise, particularly tiredness or fatigue, affecting quality of life and expected to improve with thyroid hormone replacement. Such patients may not be truly 'subclinical' and a 'trial' of thyroxine treatment is warranted, as suggested in the ETA guidelines.

When biochemical SCH is identified, the ETA guideline suggests a repeat mea-

surement of both serum thyroid-stimulating hormone (TSH) and free thyroxine along with thyroid peroxidase antibodies after a 2- to 3-month interval. We agree that repeating thyroid function tests is important as many patients will normalise their TSH results and should not be treated with levothyroxine. Some will show progression to overt biochemical hypothyroidism where treatment is no doubt warranted. However, the usefulness of auto-antibodies in supporting the decision whether to start thyroxine is less clear, since although antibody-positive subjects have an increased risk of developing biochemical hypothyroidism over a prolonged follow-up [2], the decision whether to treat is based on thyroid function status and symptoms rather than on the presence of auto-antibodies.

After repeat thyroid function tests, the ETA guideline then recommends that when TSH is persistently elevated, patients should be categorised by TSH level (mild increase 4.0–10.0 mU/l, severer increase >10 mU/l) and by age (<70 years categorised as 'younger' and over 80 or 85 years as 'oldest old'). It is stated that 'age-specific local reference ranges for serum TSH should be considered in order to establish a diagnosis of SCH in older people' [1]. We

believe this advice is premature and overly complex. It is also difficult to implement, as most laboratories do not offer age-specific ranges.

The rationale underpinning the ETA recommendations comes from clinical associations of SCH in observational data sets. Cohort studies in predominantly middle-aged or young elderly subjects show increased cardiovascular mortality associated with TSH concentrations of 10.0–19.9 mU/l (adjusted hazard ratio 1.58, 95% confidence interval 1.10–2.27; compared with TSH 4.5–6.9 mU/l); however, there is no epidemiological association of SCH with increased total mortality [3]. Furthermore the epidemiological associations may be reversed in later life; SCH in those older than 80 years may be associated with improved health and survival compared with the euthyroid state [4]. This raises the possibility that thyroxine replacement for subclinical hypothyroidism could be harmful, particularly in the 'oldest old'.

There is an association of lower TSH levels with an increased risk of atrial fibrillation; subjects with SCH have a reduced risk of this arrhythmia [5]. Thyroxine treatment is also associated with an increased risk of fracture with a dose-dependent relationship [6]. Lower TSH and high-

er thyroid hormone levels are also associated with a reduced bone density and increased risk of fractures [7]. Therefore there is the potential for thyroxine treatment of SCH to cause harm due to atrial fibrillation and also to increase the risk of osteoporotic fractures.

However, the associations demonstrated in observational studies are not sufficient to prove causality and cannot fully inform decisions whether or not to initiate thyroxine treatment in clinical practice. For that we need good-quality randomised controlled trials. The Cochrane review of thyroxine replacement for subclinical hypothyroidism found 12 trials with 350 patients [8]; there was insufficient evidence to allow definitive advice for prescribing (or avoiding) treatment, including in subgroups of those with TSH concentrations above 10 mU/l or in very elderly people.

The decision on whether to initiate thyroid hormone replacement for SCH is

therefore currently finely balanced given the lack of good randomised clinical trial evidence to support decision making. As well as the possibility of benefit from treatment, there is the possibility of harm. We strongly endorse recommendations that further trials are required. Funded by the EU, we are currently recruiting subjects to the Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism Trial (TRUST) – a multicentre randomised placebo-controlled trial of levothyroxine in subclinical hypothyroidism with cardiovascular events and quality of life the coprimary outcomes (ClinicalTrials.gov NCT01660126). An additional parallel study is recruiting subjects over the age of 80, with the aim of determining whether this subgroup benefits from treatment. It is expected that the TRUST-IEMO (Institute for Evidence-Based Medicine in Old Age) collaboration will report by late 2016 and will generate

data that properly informs future evidence-based guidelines. Until then definitive guidance on initiation (or withholding) of levothyroxine will carry the risk of causing harm. Furthermore by inferring that the best process of care is already known, such guidance may negatively affect recruitment to trials such as TRUST-IEMO that are required to determine whether treatment gives net clinical benefit.

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