Therapeutics

Low-dose levothyroxine did not improve symptoms in asymptomatic older people with subclinical hypothyroidism

10.1136/ebmed-2017-110819

Simon H S Pearce,[1,2] **Earn H Gan**[1,2]

[1]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK, [2]Endocrine Unit, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Correspondence to: Professor Simon H S Pearce, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne NE1 3BZ, UK; simon.pearce@newcastle.ac.uk

Commentary on: Stott DJ, Rodondi N, Kearney PM, *et al*. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med* 2017;376:2534–44.

Context

Subclinical hypothyroidism (SCH), defined as an elevated serum thyroid-stimulating hormone (TSH) with normal circulating free thyroid hormones, is a common and frequently asymptomatic condition. SCH becomes increasingly prevalent with advancing age,[1] and current guidelines recommend no treatment for older patients with serum TSH concentrations between the upper limit of the reference range and 10 mU/L.[2] However, as numerous large epidemiological studies show an excess of cardiovascular events and/or increased mortality in patients with SCH,[3] there are important questions about whether long-term levothyroxine treatment could either ameliorate vascular risk in this population or improve symptoms of hypothyroidism.

Methods

In this study,[4] 737 individuals over the age of 65 years were recruited by screening laboratory and primary care records at centres in the UK, Eire, the Netherlands and Switzerland. Those with at least two measurements of serum TSH between 4.6 and 19.99 mU/L, separated by 3 or more months, were eligible, and equal groups were randomised in a double-blind fashion to levothyroxine or placebo. The joint primary outcome measures were change in thyroid-specific symptoms measured by the Thyroid Patient Reported Outcome (ThyPRO) questionnaire and a tiredness score after 12 months.

Findings

Seventy-six per cent of patients with SCH allocated to levothyroxine received a dose of 50 µg daily or less, with 12% taking 75 or 100 µg daily, and a further 12% discontinuing treatment before 12 months. The mean TSH in the treated group fell from 6.4 mU/L to 3.6 mU/L, and to 5.48 mU/L in the placebo group. Baseline ThyPRO symptom and tiredness scores were not abnormal, and there was no difference in either following 12 months of levothyroxine therapy compared with placebo. There was no difference in adverse events between the active and placebo groups. Only three vascular deaths were recorded during follow-up, with insufficient power to detect any difference.

Commentary

This trial fails to address the key management questions about SCH that clinicians are faced with, on several counts. First, it recruited patients with what is generally an asymptomatic condition from database records, and their symptom and tiredness scores at baseline were not abnormal. The mean baseline ThyPRO symptom scores in both groups were 17 out of a maximum score of 100 (higher score indicates worse symptoms), and remained unchanged following both levothyroxine and placebo. This compares with a Danish study showing a pretreatment ThyPRO score of 37 in patients with hypothyroidism recruited from hospital clinics, which improved to 19 following 6 months of

levothyroxine.[5] Therefore, it is unsurprising that the symptom scores did not improve. This study cannot inform the clinician who faces a symptomatic SCH patient. In addition, the study used relatively low doses of levothyroxine, with a modal dose of 50 µg daily (in 65% of treated subjects). Previous studies of SCH in younger patients have found marginal evidence for symptom improvement, even using a levothyroxine dose of 100 µg daily.[6] The serum TSH target was too liberal, with a mean TSH in the treated group of 3.6 mU/L. One current guideline recommends achieving a serum TSH of 2.5 mU/L or less in most adults before concluding that levothyroxine is not effective in improving symptoms.[1] Finally, the study had insufficient power to find differences in vascular event rates.

Implications for practice

Asymptomatic patients over 65 years of age who are found to have an elevated serum TSH are unlikely to derive symptomatic benefit from low-dose levothyroxine therapy.

Important unanswered questions remain, including whether levothyroxine could improve vascular outcomes for asymptomatic patients with SCH, and whether patients with SCH presenting with hypothyroid symptoms would have their symptoms improved by levothyroxine. Further larger and better designed studies, which are powered to detect differences in vascular outcomes, are still needed to address these commonly encountered management issues.

Contributors SHP made the first draft of the paper and EHG commented and rewrote parts of it.

Competing interests SHP received speaker fees from Merck during 2011 and 2012, and received advisory board fees from Shire and Pfizer during 2016 and 2017. EHG has no conflicts.

Provenance and peer review Commissioned; internally peer reviewed.

To cite: Pearce S H S, Gan E H. *BMJ Evidence-Based Medicine* 2018;23:39–40.

References

1. **Hollowell JG**, Staehling NW, Flanders WD, *et al*. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): national health and nutrition examination survey (NHANES III). *J Clin Endocrinol Metab* 2002;**87**:489–99.
2. **Pearce SH**, Brabant G, Duntas LH, *et al*. 2013 ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J* 2013;**2**:215–28.
3. **Rodondi N**, den Elzen WP, Bauer DC, *et al*. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 2010;**304**:1365–74.
4. **Stott DJ**, Rodondi N, Kearney PM, *et al*. Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med* 2017;**376**:2534–44.
5. **Winther KH**, Cramon P, Watt T, *et al*. Disease-specific as well as generic quality of life is widely impacted in autoimmune hypothyroidism and improves during the first six months of levothyroxine therapy. *PLoS One* 2016;**11**:e0156925.
6. **Razvi S**, Ingoe L, Keeka G, *et al*. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab* 2007;**92**:1715–23.

BMJ Evidence-Based Medicine

Low-dose levothyroxine did not improve symptoms in asymptomatic older people with subclinical hypothyroidism

Simon H S Pearce and Earn H Gan

*BMJ EBM*2018 23: 39-40
doi: 10.1136/ebmed-2017-110819