Subclinical hypothyroidism in community-dwelling older people: consequences and treatment outcomes

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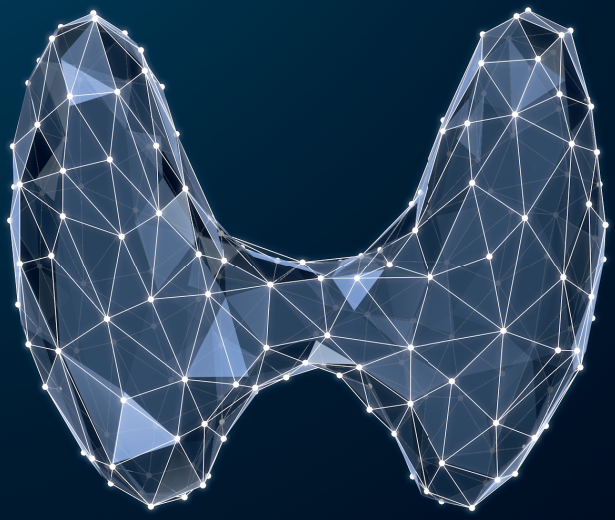

Chapter 10

English Summary

The thyroid gland plays a crucial role in regulating nearly all bodily processes. A particular state of thyroid function, dubbed subclinical hypothyroidism (with high thyroid-stimulating hormone [TSH] and normal free thyroid hormone [fT4] in blood tests), is often asymptomatic or accompanied with unspecific symptoms. Subclinical hypothyroidism becomes more prevalent with advancing age and it is unclear how this condition should be interpreted in community-dwelling older people (arbitrarily 65 years and older). The consequences and treatment considerations regarding subclinical hypothyroidism in community-dwelling older people are long-debated subjects. In the absence of robust and conclusive scientific evidence, and with decades of arguably trial-and-error experimentation with levothyroxine treatment (artificial thyroid hormone), opinions about whether monitoring is required and whether subclinical hypothyroidism requires levothyroxine treatment or not are spread out wide and bolstered.

Some observational studies have associated subclinical hypothyroidism in older people with negative consequences such as diminished physical and cognitive function, increased risk of depression, increased risk of progression to more serious thyroid disease and even increased mortality. In part because of these potential negative consequences, some patients are treated with levothyroxine whilst others are not. At the same time, other observational studies fail to arrive at the same conclusions or find evidence to the contrary. Only a few trials have investigated whether thyroid hormone supplementation provides any benefits. Most studies however suffer from key issues, such as low numbers of participants, various age ranges, different laboratory reference ranges and short follow-up times that limit generalizability to the vast majority of community-dwelling older people with subclinical hypothyroidism.

To improve the care of subclinical hypothyroidism in older people, the aims of this thesis were two-fold:

1. to establish whether subclinical hypothyroidism in older people is associated with clinically relevant outcomes and biologically relevant outcomes that may render it a neutral, beneficial or detrimental condition.
2. to investigate if levothyroxine treatment for subclinical hypothyroidism in older people provides long-term benefits.

Part 1: Consequences of subclinical hypothyroidism in older people

In the first part of this thesis, we first established whether subclinical hypothyroidism is actually associated with negative outcomes in community-dwelling older people, that warrant any physician action.

In **Chapter 2** we set out to measure clinical health outcomes in 4 prospective cohorts including 2,116 participants aged 80 years and older in the Netherlands, New Zealand, United

Kingdom and Japan. We found that participants with subclinical hypothyroidism scored the same in activities of daily living, cognition, mood and physical function as their euthyroid counterparts, and did not suffer from increased mortality. Moreover, no differences in functioning were found after 5 years of follow-up. The influence of subclinical hypothyroidism on clinically relevant outcomes therefore seems limited in community-dwelling older people.

It has been demonstrated that the presence of antithyroperoxidase antibodies (TPOAb) is associated with autoimmune thyroid diseases such as Hashimoto's thyroiditis or Graves' disease. Antibodies are usually produced by the human body to fight of harmful infections, but TPOAb target the thyroid gland instead. It is thought that TPOAb positivity is a predictor of progression to overt hypothyroidism and that these cases of subclinical hypothyroidism may actually suffer more negative consequences. Therefore, in **Chapter 3** we investigated the associations between TPOAb levels and clinical outcomes in community-dwelling older people in the Leiden 85-plus Study; a cohort including 488 residents of Leiden aged 85 at the start of the study. Although TPOAb positivity was indeed associated with higher thyroid-stimulating hormone levels at baseline and after 3 years of follow-up, it was not associated with an increased risk of change in thyroid function (i.e. progression to overt hypothyroidism), nor with activities of daily living, mood and physical function. Contradictory to expectations, positive TPOAb predicted a slight survival benefit after 10-years, but it is unlikely that this is caused by thyroid hormones. Accordingly, the consequences of positive TPOAb for clinically relevant outcomes in subclinical hypothyroidism in older people is minimal.

In observational studies subclinical hypothyroidism is often found in co-occurrence with biological outcomes such as anaemia. Therefore, in **Chapter 4** we analysed the data from 16 international longitudinal cohort studies in the Thyroid Studies Collaboration consisting of over 23,000 participants aged 65 years and older, who had measurements of thyroid function and anaemia. Although the chance of having anaemia at the start of the study was slightly higher in the presence of subclinical hypothyroidism, there was no increased risk of developing anaemia over almost six years of follow-up time.

The results from the first part of the thesis demonstrate that subclinical hypothyroidism in community-dwelling older people is not associated with clinically relevant or biologically relevant outcomes.

Part 2: Treatment outcomes for subclinical hypothyroidism in older people

In the second part of the thesis, the focus was shifted from observational to experimental studies, in order to discover if levothyroxine treatment for subclinical hypothyroidism in older people provided long-term benefits in clinically or biologically relevant outcomes.

In the TRUST study, an international randomised controlled trial involving 737 community-dwelling adults with subclinical hypothyroidism aged 65 years and older, we sought to understand whether levothyroxine treatment for at least one year would provide clinical benefits. In this study, written down in **Chapter 5,** we found that there was no change in hypothyroid symptoms, tiredness, adverse events or a battery of secondary clinical outcomes after at least one year of treatment.

Because thyroid function changes with age, we hypothesised that the effects may be profoundly different in the oldest old. Therefore in **Chapters 6** and **7** we investigated any potential clinical benefits in even older adults; aged 80 years and older. To allow for a joint analysis of all participants aged 80 years and older, the IEMO 80-plus study was designed as a complementary trial to the TRUST study, described in **Chapter 6**. In **Chapter 7** the results demonstrate that treatment with levothyroxine in participants aged 80 years and older was not associated with changes in symptoms, tiredness, adverse events or an extensive set of secondary clinical outcomes after at least one year of treatment. This is in line with the results from **Chapter 5**.

Finally, in **Chapter 8**, we studied whether levothyroxine treatment was associated with changes in biological outcomes – i.e. the occurrence or resolution of anaemia, or any change in haemoglobin at all. By again combining the data from the TRUST and IEMO 80-plus thyroid trials we discovered that there was no change in anaemia status after a minimum of one-year levothyroxine treatment for subclinical hypothyroidism in older people.

The results from the second part of the thesis show that levothyroxine treatment does not lead to benefits in clinically or biologically relevant outcome measures. These results do not support routine treatment for all older adults with subclinical hypothyroidism.

Discussion

All evidence considered, it may be concluded that in community-dwelling populations of older people, the state we currently describe as subclinical hypothyroidism is not a disease but a strictly biochemical diagnosis that is not associated with detrimental nor beneficial health outcomes. Treatment with levothyroxine does not provide benefits. It is important to keep in mind that the conclusions of this thesis do apply to the vast majority of community-dwelling older people, but may not be generalisable to certain specific subgroups of older people with subclinical hypothyroidism, such as those under the care of a medical specialist.

Physicians could play a crucial role by preventing medicalisation, unburdening patients from lifelong invasive diagnostic schemes, exercising restraint in pharmaceutical management and reducing potential overtreatment. Laboratory screening protocols may need to be updated

(and TSH-reflex testing potentially even reversed after additional research) and deprescribing studies should investigate if current levothyroxine users can taper and stop treatment without harm. Additionally, future studies should investigate whether the findings of this thesis may be generalised to more uncommon populations and to younger age groups. Finally, more research will be needed to explore patient values, preferences and perspectives about subclinical hypothyroidism, age-adjusted laboratory reference ranges and the biology of the ageing thyroid. We encourage guideline committees to update the guideline recommendations to realign with the findings, conclusions and recommendations of this thesis.

For now, the findings from this thesis suggest that the best medical care is provided by employing a more conservative management style, reducing thyroid function testing and levothyroxine prescriptions, but that there is still much left to be discovered.