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

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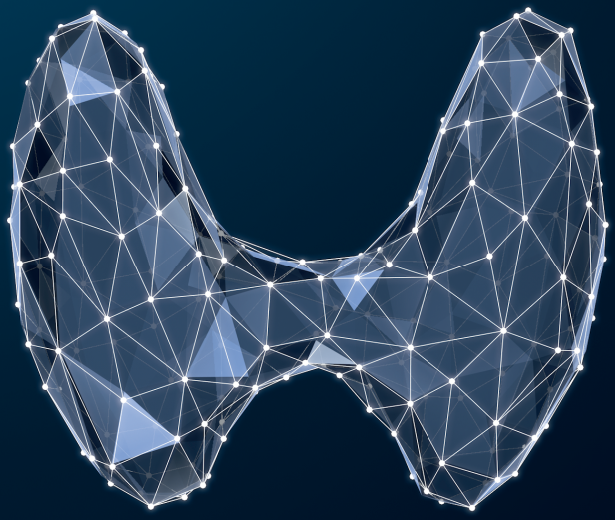

Chapter 1

General introduction

The consequences and treatment considerations regarding subclinical hypothyroidism in community-dwelling older people (arbitrarily 65 years and older) are long-debated subjects.[1] In the absence of robust and conclusive scientific evidence, and with decades of arguably trial-and-error experimentation with levothyroxine treatment, opinions about whether monitoring is required and whether it requires levothyroxine treatment (artificial thyroid hormone) or not, are spread out wide and bolstered. Patients, physicians and researchers often adhere to different schools of thought and can be found voicing opinions on both ends of spectra. For instance, some consider subclinical hypothyroidism to be consequential to health and longevity, others don't. Some believe it is a natural evolutionary process that may even be protective, others feel it's a sign of pre-clinical thyroid dysfunction. Finally, some consider treatment with levothyroxine to be necessary, others maintain that the condition is best left alone. Decades of research and experience have to date not been able to bridge these divides. To help address these issues, this thesis set out to investigate whether older, community-dwelling people with subclinical hypothyroidism have a neutral, beneficial or detrimental condition, and whether treatment with levothyroxine is beneficial.

Thyroid function

The thyroid gland, a small organ producing thyroid hormones, is found in all vertebrates, and plays a crucial role throughout an organism's lifecycle by regulating all metabolic processes.[2] It is often underappreciated when functioning normally. However, it becomes a powerful modifier of health and life when under- or overactive. For instance, in animals physiologic (non-diseased) low blood levels of thyroid hormone are implicated as the cause of longevity in long-lived species of squirrels and bats,[3-6] while physiologic high levels signals tadpoles to metamorphose into frogs.[7]

However, pathophysiologic (diseased or abnormal) low blood levels of thyroid hormones unquestionably lead to unhealthy fetal brain development[8] whilst pathophysiologic high levels, especially when all stored hormone is released at once, is not rarely fatal.[9] Differentiating between normal and diseased states of thyroid function is vital to good health and, although the effects of thyroid (dys-)function have been recorded and investigated for at least 4700 years,[10] the exact role in human health remains ever to be elucidated.

Thyroid hormone synthesis starts with cleaving thyroglobulin into up to 120 individual tyrosine molecules.[11] With the help of the thyreoperoxidase (TPO) enzymes, iodine atoms provided through the diet and the now freed tyrosine molecules, are combined to produce the two primary thyroid hormones thyroxine (T4, with 4 iodine atoms) and triiodothyronine (T3, with 3 iodine atoms), ready to enter the circulation.

The production and secretion of thyroid hormones are under strict regulation (figure 1). One particular section of the brain, the hypothalamus, acts much like a thermostat to the central heating of a house. It determines the set-point of thyroid hormone regulation by releasing Thyrotropin-Releasing Hormone (TRH) in specific intervals. The secreted TRH stimulates a second organ in the skull, the pituitary gland, to release its stimulatory Thyroid-Stimulating Hormone (TSH or Thyrotropin). Additionally, both organs respond to changing blood levels of circulating T3 and T4. When secreted TSH binds with the TSH-receptor on the thyroid follicles the thyroid gland releases its T4 and T3 in a 14:1 ratio.[12] However, since 99.98% of T4 and 99.70% of T3 is immediately bound by proteins in the blood only 0.02% of free T4 (fT4) and 0.3% of free T3 (fT3) is active throughout the body.[13] Only the free serum T4 and T3 concentrations determine the biological activity. The increased concentrations of fT3 and in particular fT4 then signal the hypothalamus and pituitary gland to decrease their production of TRH and TSH respectively and this eventually decreases the availability of circulating levels of fT4 and fT3, maintaining balance.

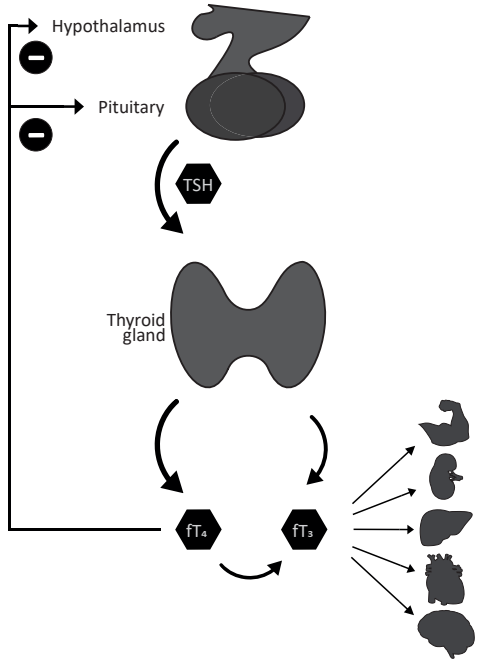

Figure 1. The Hypothalamic-Pituitary-Thyroid Axis. Serum measurements of TSH and fT4 are used by physicians as proxies of thyroid function. Adapted from [15].

In virtually all tissues in the human body binding of T3 increases the speed of protein synthesis and substrate turnover, effectively making the cell, tissue or organ work harder.[14] A majority of the locally available fT3 is not dependent on the secreted fraction from the

thyroid gland however, which is after all very small, but on the conversion of fT4 to fT3 in the liver and kidneys through deiodinase enzymes that allow for organ-specific regulation of extrathyroidal fT3 production. Because of these tissue-specific differences in fT3, clinicians mostly rely on the measurement of TSH and fT4 to assess overall thyroid function in the entire body and to weigh treatment modalities.

Abnormal thyroid function

If, however, the hypothalamic-pituitary-thyroid axis functions abnormally, and an overproduction (hyperthyroidism) or underproduction (hypothyroidism) of thyroid hormone exists, overt thyroid disorders start to emerge. The multifarious effects of thyroid hormones in all organs and tissues explain the pleiotropic clinical signs and symptoms. For instance, in overt hyperthyroidism signs and symptoms may include palpitations, tremors, anxiety, weight loss, heat intolerance, mood instability and shortness of breath.[16] Conversely, overt hypothyroidism may manifest predominantly with fatigue, cold intolerance, weight gain, anaemia, constipation and dry skin.[17] Since thyroid status cannot always be predicted from the often non-specific clinical signs and symptoms, a clinician will, when thyroid disease is suspected, order laboratory analyses of serum samples to investigate whether thyroid dysfunction is present and in what form. Normal thyroid function (euthyroidism) is defined biochemically according to the local laboratory reference ranges (normal reference ranges for TSH commonly between 0.4 and 4.0 mIU/L and for fT4 commonly between 9.0 and 24.0 pmol/L) although inter-individual variances are common with a genetically determined unique TSH and fT4 setpoint.

Overt or clinical thyroid dysfunction is diagnosed when serum analyses deviate from the normal reference ranges, irrespective of the underlying cause. Overt hypothyroidism is defined as a TSH above the laboratory reference range with an fT4 below the laboratory reference range. Overt hyperthyroidism is the exact opposite; defined as a low TSH with fT4 above the reference ranges. In general populations of iodine-sufficient parts of the world the prevalence of overt hypothyroidism ranges from 0.2% to 5.3% and for overt hyperthyroidism ranges from 0.2% to 1.3%.[18] Since the symptoms of overt thyroid disease can often be resolved and serum levels normalised, most international guidelines recommend routine and sometimes lifelong treatment of overt hypothyroidism with levothyroxine administration[19] and treatment of overt hyperthyroidism with either drugs, surgery or radioactive iodine administration.[20]

Subclinical hypothyroidism in old age

In between the two overt thyroid function disorders, but different from the normal euthyroid state, we define two additional subclinical thyroid dysfunctions that are much more common in the community. Subclinical hypothyroidism, defined as TSH levels above the reference

range but with normal circulating fT4 levels is prevalent in 4.0% to 15.4% of the general population[22-25] and patients are generally asymptomatic.[26] Subclinical hyperthyroidism is defined as TSH levels below the reference range but with normal circulating fT4 levels and is prevalent in 0.7% to 12.4% of the community.[25] At the time of writing this thesis, international experts have not reached a consensus on whether or how these subclinical thyroid diseases require medical treatment.

It has long been recognised that thyroid function disorders appear to occur more frequently in older people, in particular subclinical hypothyroidism (figure 2). The prevalence of subclinical hypothyroidism in women aged 60 years and older may be as high as 20% in the general population,[21] higher than that of overt hypothyroidism (0.2-5.3%), subclinical hyperthyroidism (0.6-9.8%) and overt hyperthyroidism (0.8-1.3%) combined. With increasing age more changes in thyroid anatomy, function and outcomes can be detected, yet how much this influences health and longevity is not fully understood.

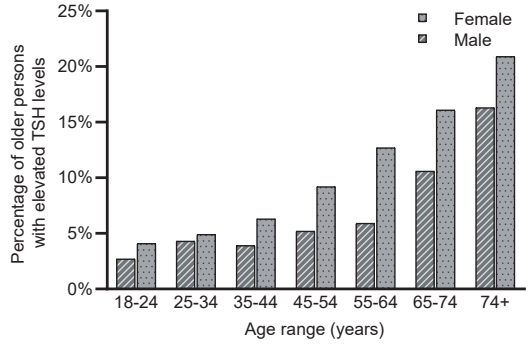

Figure 2. Percentage of community-dwelling older people with elevated TSH levels by age range. Adapted from [21].

Anatomically, over time, the thyroid gland reduces in volume, decreases its iodine uptake and decreases its T4 secretion.[27] Contrastingly, T4 and T3 clearance is decreased compensating for the loss of production. The natural course of thyroid function shows more variation in old age, with subclinical thyroid disorders being found more often, yet often reverting to a euthyroid state without intervention as well.[28] In older people clinical signs and symptoms are generally even more subtle, atypical or absent compared to younger age groups, rendering them unhelpful in physician decision making.[29] If findings are present at all these are not seldomly attributed to old age or confused with other comorbidities. Earlier studies yielded greatly conflicting results, with both increased, neutral and decreased risks or odds, for associations between subclinical hypothyroidism and cardiovascular disease, cognition, mood, lipid metabolism, quality of life, fractures and cause-specific and all-cause mortality. [30-32]

Subclinical hypothyroidism in old age: physicians' predicament

The medical care for community-dwelling older people with subclinical hypothyroidism is not only the responsibility of General Practitioners (GPs) but may be accommodated by different medical practitioners (including but not limited to family physicians, endocrinologists, internists and thyroidologists). In this thesis the combined group of professionals that deal with community-dwelling older people with subclinical hypothyroidism will be referred to as physicians henceforth.

In light of the arguments presented in the aforementioned paragraphs, physicians often struggle with managing subclinical hypothyroidism in older people. While patients with an elevated TSH laboratory finding look to their physician for support, without compelling clinical trial experience, uncertainty about the prognosis and with guidelines offering equivocal directions, physicians demonstrate significant variability in diagnostic and treatment strategies;[33] 'Should I handle this elevated TSH level finding as a disease? Or do I reassure my patient that this is normal and does not explain any potential symptoms? Do I monitor thyroid function over time? Or should I start levothyroxine treatment instead?'.

In an ageing population, it is to be expected that physicians will have to deal with similar dilemmas more and more. As the numbers of older people with subclinical hypothyroidism rise, with better access to their lab results, more influence from sometimes indiscriminate online sources and backing from assertive advocacy groups, lacking evidence-based support as a physician may shift the balance of the narrative and increase tension of the doctor-patient relationship. Simultaneously physicians have a societal responsibility to allocate the limited healthcare resources available (i.e. time, money, referrals and manpower) equally and just, based on the available evidence base and agreements with healthcare insurers and the health ministries. Evidently, future physicians would benefit greatly from scientifically grounded guiding principles and treatment strategies.

Aim

The overall aim of this thesis is to establish the effects of subclinical hypothyroidism on clinically and biologically relevant outcomes, and the effects of levothyroxine treatment on similar endpoints, in community-dwelling older people.

Research objectives

1. To establish whether subclinical hypothyroidism in older patients is a neutral, beneficial or detrimental condition by establishing if subclinical hypothyroidism in older people is associated with:
   a. clinically relevant outcomes
   b. biologically relevant outcomes
2. To investigate if levothyroxine treatment for subclinical hypothyroidism in older people provides long-term benefits in clinically or biologically relevant outcomes

Part 1: Consequences of subclinical hypothyroidism in older people

The first part will focus on observational studies and aims to establish whether subclinical hypothyroidism in older patients is a neutral, beneficial or detrimental condition by establishing if subclinical hypothyroidism in older people is associated with clinically relevant outcomes or associated with biologically relevant outcomes.

Chapter 2 discusses the findings from an extensive Individual Patient Data Meta-Analysis conducted in cohorts of people aged 80 years and older from the Netherlands, the United Kingdom, New Zealand and Japan. The study focuses on discovering associations between thyroid dysfunction as assessed traditionally using TSH and fT4 (i.e. overt hypothyroidism, subclinical hypothyroidism, subclinical hyperthyroidism and overt hyperthyroidism) and activities of daily living, cognitive function, physical function, depressive symptoms and mortality. Its advantage compared to earlier studies is the harmonization and standardization of determinants, including TSH and fT4, and outcomes.

In **chapter 3** we examine associations between elevated levels of thyreoperoxidase antibodies, a biological marker commonly found in patients with thyroid dysfunction, and mortality, incident thyroid disease, changes in physical function, disability in activities of daily living, cognitive function and depressive symptoms using the data from the Leiden 85-plus Study. In **chapter 4**, an Individual Patient Data Meta-Analysis using data from sixteen international cohorts, we investigate cross-sectional odds of having, and longitudinal hazards of developing, anaemia in different categories of thyroid dysfunction. As well as stratifying the findings for different sexes, ethnicities and ages.

Part 2: Treatment outcomes for subclinical hypothyroidism in older people

The second part of the thesis will shift the focus to experimental studies and aims to discover if levothyroxine treatment for subclinical hypothyroidism in older people provides long-term benefits in clinically or biologically relevant outcomes

Chapter 5 presents the results from an international randomised controlled trial (TRUST study), focusing on the effects of levothyroxine treatment for subclinical hypothyroidism in >65-year-old people. In **chapter 6** and **chapter 7** we describe the design and results of a complementary international randomised controlled trial aimed specifically for the treatment of people with subclinical hypothyroidism aged 80 years and older in the IEMO 80+ thyroid trial. **Chapter 8** presents the results from levothyroxine treatment for subclinical hypothyroidism on haemoglobin levels in people aged 65 years and older using data from both the TRUST study and IEMO 80+ thyroid trial.

Finally, **chapter 9** presents a summary and discussion of the main findings of this thesis, complete with implications for physician practice and future perspectives for thyroid research.

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