Ageing and endocrinology 3

Clinical aspects of thyroid function during ageing

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Globally, populations are ageing at a rapid rate. The increase in the number of older citizens is accompanied by an increased prevalence of thyroid dysfunction, one of the most common disorders in older people. However, the diagnosis of thyroid dysfunction in older people is hindered by several factors, including the scarcity of thyroid dysfunction symptoms in older people. We describe the physiological changes in thyroid function that occur with increasing age, focusing on literature regarding changes in thyroid function test results in older populations. We also discuss treatment considerations for clinical and subclinical thyroid dysfunction according to international guidelines for older people. Finally, we discuss the relationship between variations in thyroid function and common diseases of old age including cardiovascular disease, osteoporosis, cognitive impairment, and frailty and suggest directions for future research.

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Introduction

Globally, mean life expectancy (ie, the average years lived at a population level) has steadily increased and populations are ageing at a rapid rate.[1] The increase in the number of older citizens is accompanied by an increased prevalence of morbidity, with thyroid dysfunction being one of the most common disorders, reflected in a prevalence of up to 20% in community-dwelling individuals aged 65 years and older.[2] It is not known whether this increase in the prevalence of thyroid dysfunction also indicates pathophysiology in need of treatment. Some studies indicate that low thyroid function is associated with favourable clinical outcomes, including a longer lifespan and a lower risk of cognitive impairment in older adults. Several factors can hinder the diagnosis of thyroid dysfunction in older people, including comorbidities, non-thyroidal illness, concomitant drug use and physiological changes in the hypothalamic-pituitary-thyroid axis.

In this Review, we discuss physiological changes in thyroid function that occur with increasing age, the epidemiology and treatment of thyroid dysfunction in the older population, and the relationships between variations in thyroid function and diseases of old age. There is no clear age cutoff to define older people, and the cut-offs that were chosen in the articles that we searched depended on many aspects, including the mean age of the population studied and historical considerations (eg, age of retirement). Thyroid malignancies are not part of this review and have been discussed extensively elsewhere.[3] Furthermore, we only briefly touch on biological mechanisms related to thyroid function, but refer to other reviews for more extensive information on thyroid hormone signalling during maturity and ageing.[4]

Thyroid function during ageing

Changes in the hypothalamic-pituitary-thyroid axis and regulation of thyroid hormone action

The thyroid gland produces the thyroid hormones thyroxine (T4) and triiodothyronine (T3) in approximately a 14-to-1 ratio.[5] Circulating thyroid hormone concentrations are tightly regulated by the negative feedback mechanism of the hypothalamic-pituitary-thyroid (HPT) axis, through secretion of thyrotropin-releasing hormone from the hypothalamus and thyroid-stimulating hormone (TSH) from the pituitary. Thyroid hormone action is crucial for the function of many organs and tissues; most notably, the cardiovascular system, bones, and brain. Beyond circulating concentrations, transport (ie, by monocarboxylate transporters [MCTs] 8 and 10) and metabolism (ie, through activity of the three deiodinase [DIO] enzymes) of thyroid hormones are organ-specific and cell-specific. During ageing, changes occur in thyroid structure and function that affect thyroid hormone production, metabolism, transport, and action. The size of the thyroid gland decreases in older people without nodular disease and the position is more caudal than in younger individuals.[6,7] Most evidence regarding changes in thyroid hormone secretion, metabolism, and transport with increasing age comes from rats and mice (table 1).[8–11] Decreased secretion of thyroid hormones and reduced liver DIO1 activity is seen in rats that are ageing, despite similar TSH plasma concentrations. In old male rats (aged 24 months), MCT8 concentrations are reduced in the liver, but not in the kidney.[10] In a mouse model of accelerated ageing, metabolism and signalling of thyroid hormones are altered in the liver and kidney, with decreased DIO1 and increased DIO3 expression, but are largely preserved in the heart, muscle, and brain.[11]

Changes in thyroid function test results

Most[12–14] but not all[15,16] cross-sectional population and laboratory-based studies show a higher mean TSH concentration in older participants. In contrast, older studies[17] in highly selected groups of healthy older participants suggest an age-dependent decline in TSH secretion. Differences between these studies are probably due to differences in current and historical iodine intake, as well as selection criteria used in the older studies.[15] So far, only three prospective analyses[18–20] of changes in thyroid function with age have been published, each with slightly different results (table 2). A US study by Waring

and colleagues[18] with 843 participants with a mean age of 72 years showed an increase in TSH (0·34 mIU/L; 13%) and free T4 (FT4) concentrations (0·26 pmol/L; 1·7%) over a median follow-up of 13 years. A prospective study by Bremner and colleagues[19] in Australia with 908 participants with 13 years of follow-up showed that TSH increased by an average of 0·32 mIU/L, with the largest increase observed in participants older than 60 years, but FT4 concentrations did not change. Lastly, a study[20] from the Netherlands by Chaker and colleagues with 1002 participants with a mean age of 67 years showed no overall change in TSH concentrations over a median follow-up of 6·5 years, irrespective of age at first measurement, with an increase in FT4 concentrations which was more prominent in older people, especially in those older than 65 years. Information on changes in T3 concentrations with increasing age is scarce and non-thyroidal illness can impede adequate collection of this information. In their US study, Waring and colleagues[18] showed a 13% decrease in T3 concentrations over a follow-up period of 13 years in community-dwelling older people, even when only including a cohort of people without thyroid disease in their analysis.

Circulating thyroid hormone concentrations are regulated by the HPT axis with a unique TSH and FT4 set point for each individual.[21] It has been reported that increasing age modifies the relation between TSH and FT4. Several studies[13,22,23] suggest that individuals aged 65 years and older have a blunted pituitary response to hypothyroidism. The relation between TSH and FT4 remains complex and the changes that occur with age and the differences within subgroups require further research.

	DIO1	DIO2	DIO3	MCT8	T3	T4
Liver	↓	..	↑	= or ↓	↓	↓
Kidney	↓	..	↑	=	↓	↓
Heart	..	= or ↑	..	..	=	=
Muscle	..	=	= or ↓	..	=	=
Brain	..	=	= or ↓	..	=	=
Pituitary	↑	↑	..	..	= or ↑	..

DIO=deiodinase. MCT8=monocarboxylate transporter. T3=triiodothyronine. T4=thyroxine. ↓Denotes decrease. ↑Denotes increase. =Denotes no change in expression with ageing. ..Denotes no available evidence.

Table 1: **Observed changes in tissue-specific thyroid hormone concentrations, metabolism, and transport with increasing age from animal studies[8–11]**

Thyroid dysfunction during ageing

Diagnosis and epidemiology of thyroid disease in older populations

Thyroid dysfunction is a biochemical diagnosis that relies on the reference ranges of thyroid function tests. Clinical hypothyroidism is defined by serum TSH concentrations above the reference range and serum FT4 concentrations lower than the reference range. With subclinical hypothyroidism FT4 is still within the reference range. For hyperthyroidism, TSH concentrations are lower than the reference range and FT4 or T3 concentrations are above the reference range. With mild or subclinical hyperthyroidism FT4 and T3 are still within the reference range.[24] The reference range of TSH depends on the assay used and the population in which it has been measured, but 0·4–4·5 mIU/L is most commonly used.[25] Some experts suggest use of age-specific reference ranges for TSH, advocating a shift towards the upper limits of TSH concentrations. When age-specific reference ranges are applied, a reclassification from abnormal to normal thyroid function occurs in older people.[14,18,26,27] However, it is unclear whether this reclassification is generalisable to other subgroups, (eg, subgroups with different iodine status). It is also unclear if age-associated changes in thyroid function are adaptive and whether a reclassification based on population distributions will lead to better outcomes if applied as a treatment cutoff, or if a subset of older patients with mild abnormalities as defined by current reference ranges have thyroid disease that would benefit from treatment.

The prevalence of clinical hypothyroidism in the general population is estimated to be 0·2–5·3% and the prevalence of subclinical hypothyroidism is estimated to be 4–15%.[28–32] For clinical hyperthyroidism the prevalence is estimated to be 0·8–1·3% and for subclinical hyperthyroidism the prevalence is estimated to be 0·6–9·8%.[33,34] The prevalences of both hyperthyroidism and hypothyroidism increase with increasing age. Progression from subclinical to clinical hypothyroidism is faster in patients who are positive for anti-thyroid antibodies (4·3% per year for female patients who are positive for anti-thyroid antibodies *vs* 2·6% per year for female patients who are negative for anti-thyroid antibodies),[32] with thyroid peroxidase antibody positivity more prevalent in older people than in younger people. Progression from subclinical to clinical hyperthyroidism due to Graves' disease occurs more often in

	Country	Number of participants	Follow-up (years)	Mean age (years)	Proportion of women (%)	Change in TSH concentration (%)	Change in FT4 concentrations (%)	Change in T3 concentrations (%)
Waring, 2012	USA	843	13 years	72	60·9%	+13%	+1·7%	–13%
Bremner, 2012	Australia	908	13 years	45·5	46·6%	+13%	No change	NA
Chaker, 2016	Netherlands	1002	6·5 years	67·2	55·9%	No change	+26%*	NA

TSH= thyroid-stimulating hormone. FT4=free thyroxine4. T3=triiodothyronine. *In participants older than 65 years.

Table 2: **Changes in thyroid function test results over time observed in three longitudinal studies[18–20]**

older patients,[35] although the incidence of Graves' hyperthyroidism is not higher in older patients. The distribution of causes of thyroid disease differ between older and younger individuals. Toxic multinodular goitre and toxic adenomas are more often a cause of hyperthyroidism in older individuals than in younger individuals, especially in iodine-deficient areas of the world.[36]

Subgroups at risk of thyroid disease

Older people as a group are at an increased risk of developing thyroid disease, with women having the highest risk. Thyroid disorders have more often been described in older patients with specific autoimmune diseases (eg, type 1 diabetes), type 2 diabetes,[37] chronic kidney disease,[38] and gastrointestinal diseases (eg, bile stones),[39] amongst others. For many of these subgroups it has not been established whether the reported associations are due to coexistence in older people, shared pathophysiological pathways, or causal effects of thyroid function on several phenotypes or vice versa.

Changes that are not directly related to thyroid dysfunction can also contribute to an increase in prevalence and incidence of thyroid disease in older individuals. In the past decades, certain conditions (eg, psychiatric illnesses) have been diagnosed and treated more often in older patients than in younger patients, leading to an increased risk of medication-induced thyroid dysfunction in this subgroup, caused, for example, by amiodarone, tyrosine kinase inhibitors, or immune checkpoint inhibitors.

Challenges in the diagnosis of thyroid disorders in older patients

Challenges in the diagnosis of thyroid disorders in older patients include changes in thyroid physiology, an increased prevalence of non-thyroidal illness, co-morbidities, and medication use, and differences in clinical presentation of thyroid disease in older patients compared with younger patients.

In non-thyroidal illness, plasma concentrations of T3 and T4 decrease whereas TSH concentration is usually within the normal range or below. However, TSH concentration can be elevated in the recovery phase. Non-thyroidal illness typically presents in severely ill individuals, but has also been described in chronically ill patients.[40] In hospitalised and severely ill patients the presence of non-thyroidal illness can hinder or falsely lead to the diagnosis of thyroid disease. Measuring thyroid function again after full recovery is advised,[41,42] unless thyroid disease is suspected as the cause of illness.

Drugs can also alter the effects of thyroid hormones without causing thyroid disease. Oral oestrogen, raloxifene, tamoxifen, and glucocorticoids affect concentrations of thyroxine-binding globulin, and aspirin, non-steroidal anti-inflammatory agents, and heparin affect proteins that bind to thyroid hormones. We refer to other reviews for more information concerning drugs that can affect thyroid function or thyroid function tests.[43]

A study[44] from France with 1572 patients diagnosed with hyperthyroidism showed that symptoms of hyperthyroidism were less frequent in older patients (≥65 years) than in younger patients, except for cardiac dysrhythmias such as atrial fibrillation. In their cross-sectional study, Boelaert and colleagues[45] reported that more than 50% of older patients (≥61 years) with hyperthyroidism presented with very few symptoms of hyperthyroidism (two or less), compared with 30% of younger patients. The prevalence of most signs and symptoms was lower in patients older than 60 years, except for weight loss, shortness of breath, and atrial fibrillation. A study[46] from Denmark with 140 patients diagnosed with autoimmune hypothyroidism and a control group of 560 participants showed a good predictive value of a hypothyroidism composite symptom score in patients younger than 50 years (area under the receiver operating characteristics [AUROC] curve of 0·91 in young men), but poor predictive value in older patients, especially women older than 60 years (AUROC curve 0·64). These studies suggest that the presentation of thyroid dysfunction is often subtle in older individuals, and that clinicians should readily test TSH concentrations in this population.

Thyroid function and age-associated diseases

Various studies have shown that there is an association between variations in thyroid function and deleterious or protective outcomes in older people and animal models. This association suggests that thyroid hormones have a central role in longevity.[47] Overt thyroid dysfunction is always treated upon diagnosis, and therefore observational studies have examined outcomes associated with variations in thyroid function in the context of subclinical thyroid dysfunction or even within the reference range (table 3).[4]

	TSH	FT4
Ischaemic heart disease	=	= or ↑
Cerebrovascular disease	=	↑
Diabetes mellitus	↑	↓
COPD	..	..
Dementia	= or ↓	= or ↑
Vision impairment	=	↑
Hearing impairment	..	..

TSH=thyroid-stimulating hormone. FT4=free thyroxine. COPD=chronic obstructive pulmonary disease. ↑Indicates a higher risk of outcome with higher values of thyroid function test. ↓Indicates a lower risk of outcome with higher values of thyroid function test. =Indicates no evidence for an altered risk associated with thyroid function test. ..Indicates insufficient evidence on the association.

Table 3: **Association of TSH and FT4 in the reference range with the most burdensome chronic non-communicable diseases in older individuals[48]**

Cardiovascular disease and mortality

Several studies describe a differential association between thyroid dysfunction and cardiovascular disease with age. An individual participant data (IPD) meta-analysis[25] from the Thyroid Studies Collaboration (TSC), a consortium of population-based cohort studies that included 55 000 participants, described an increased risk of coronary heart disease in participants with subclinical hypothyroidism with TSH concentrations higher than 10 mIU/L and an increased risk of cardiovascular mortality in participants with subclinical hypothyroidism and TSH concentrations higher than 7 mIU/L. A separate IPD meta-analysis[49] from the TSC showed an increased risk of coronary heart disease associated with subclinical hyperthyroidism. An IPD meta-analysis[50] from the TSC addressing the association of subclinical hypothyroidism and stroke showed a lower hazard ratio (HR) in participants 65 years and older as compared to younger participants. Although the two meta-analyses of subclinical hypothyroidism and hyperthyroidism and coronary heart disease suggested higher risk of coronary heart disease in younger participants (ie, those younger than 65 years of age) than in older participants, the results were not significant. An IPD meta-analysis[51] from the TSC investigating thyroid function within the reference range described no general or age-specific association of TSH or FT4 within the reference range with coronary heart disease. However, an analysis[52] from a Dutch cohort of participants with TSH and FT4 within the normal range, showed that participants with lower thyroid function, particularly lower FT4 concentrations, lived up to 3·5 years longer than participants with higher thyroid function, and up to 3·1 years longer without cardiovascular disease. There have been several interpretations for the age-dependent effects described in population studies, including changes in the HPT axis set point, a beneficial effect of a lower metabolism in older age, and survival bias, but the exact mechanism is still unknown. Information on the association of T3 concentrations with clinical outcomes and longevity is scarce.[18,53] A study from Rozing and colleagues[53] showed that familial longevity was associated with low concentrations of T3, suggesting either a role for T3 as a marker of delayed ageing, or as an adaptive mechanism to deal with other consequences of the ageing process, although low T3 concentrations have been associated with mortality in other studies. The US study of Waring and colleagues[18] did not show a relationship of T3 concentrations with mortality.

Osteoporosis and fracture risk

In an IPD meta-analysis[54] from the TSC in over 5000 participants with a median age of 72 years, subclinical hyperthyroidism was associated with increased annual bone loss at the femoral neck with a difference of 0·18% annual decline in bone mineral density (95% CI –0·34 to –0·02) as compared with euthyroid participants. Another study[55] from the TSC of over 70 000 participants indicated that subclinical hyperthyroidism was associated with an increased risk of hip fractures, spine fractures, and other fractures. Participants with endogenous hyperthyroidism and those with TSH concentrations greater than 0·1 mIU/L had the highest fracture risk. However, the relative risk of fracture did not differ by age, with an age cutoff of 75 years. A study[56] with 129 men showed no evidence that suggests a difference in risk according to the underlying cause of endogenous hyperthyroidism.

Cognitive impairment and dementia

Clinical hypothyroidism is considered a cause of reversible dementia, and routine screening for hypothyroidism is recommended as part of the medical examinations for the diagnosis of dementia.[57,58] However, it is not known to which degree the treatment of hypothyroidism results in complete regression of cognitive impairment.[59] A meta-analysis[60] of 11 prospective cohort studies reported an association of subclinical hyperthyroidism, but not subclinical hypothyroidism, with an increased risk of dementia. There was no evidence suggesting a faster decline in Mini-Mental State Examination in either condition. Two large prospective population-based cohort studies[61,62] have described an increased risk of dementia in community-dwelling older people with higher thyroid function.

Depression and quality of life

Affective disorders are among the most burdensome diseases in older populations.[48] Depression and lethargy are part of the scope of symptoms attributed to hypothyroidism.[63] However, recent studies have shown higher thyroid function to be related to increased incidence of depressive symptoms in older populations. In a Dutch study[64] of 1503 participants aged 70·6 years on average, participants with low-to-normal TSH displayed depressive symptoms more often over a study period of 8 years than participants with a high to normal TSH did, with an odds ratio for incident depressive symptoms of 1·85 (95% CI 1·10–3·11) irrespective of thyroid peroxidase antibody concentrations. In another Dutch cohort study, 606 participants with a high cardiovascular risk and a mean age of 75 years, subclinical hyperthyroidism was associated with an increase in Geriatric Depressive Scale scores after 3 years, compared with the euthyroid participants.[65]

Frailty, functional mobility, and physical performance

The ageing process results in a decrease in physiological reserve, and an increased risk of disease and mortality, leading to an increased burden of multimorbidity and polypharmacy. However, the older population is heterogeneous with respect to their level of physical, mental, and social impairments, with some individuals who are

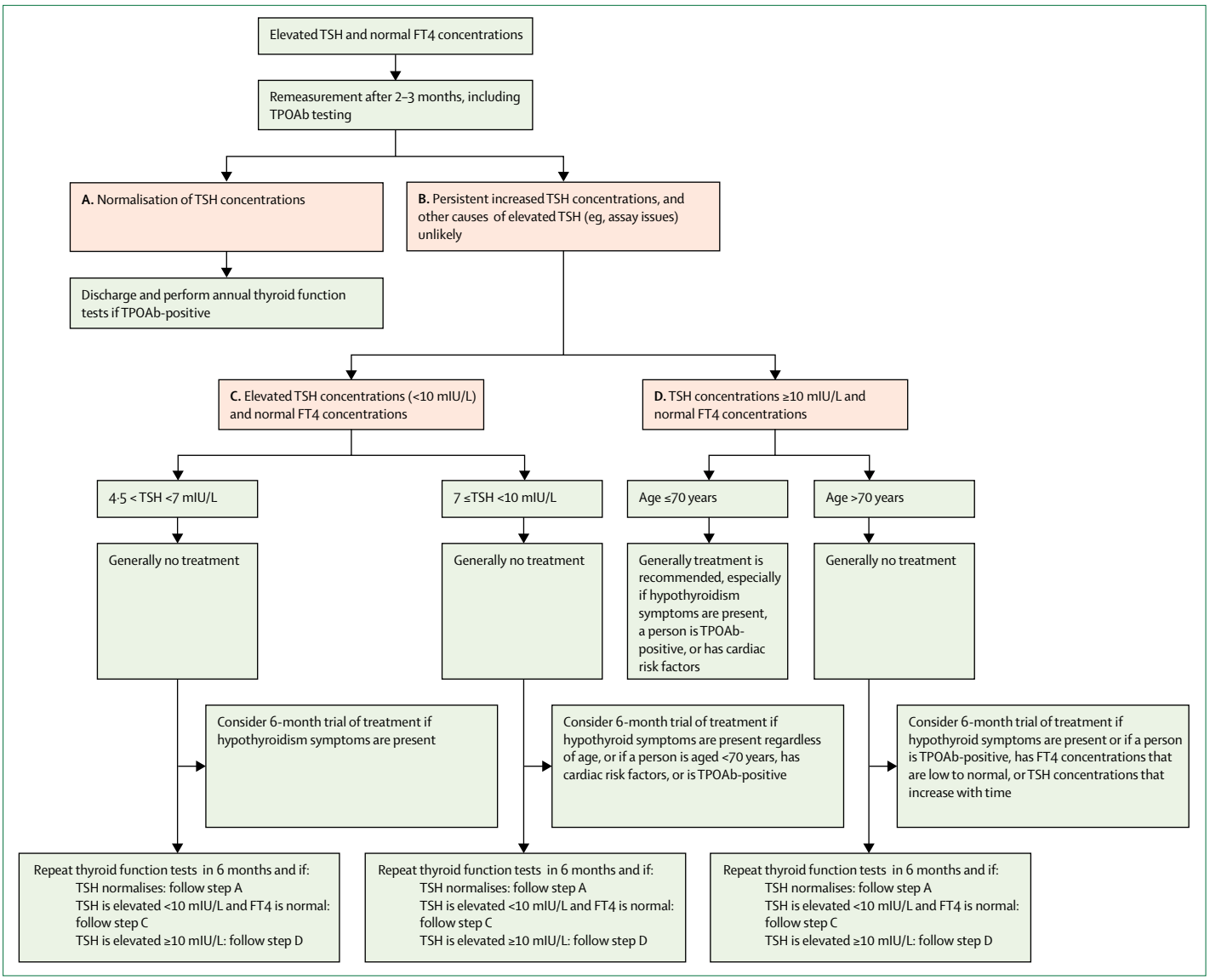

Figure 1: **Treatment algorithm for subclinical hypothyroidism**
This algorithm is based on current US and European guidelines.[41,42] However, the US guidelines do not make an explicit distinction according to age, and both guidelines do not specifiy differential management according to the degree of thyrotropin elevation below 10 mIU/L. The algorithm does not apply to pregnant women or to young women who might potentially seek pregnancy. TSH=thyroid-stimulating hormone. FT4=free thyroxine. TPOAb=thyroid peroxidase antibodies. Reproduced from reference 75 by permission of the *New England Journal of Medicine*.

very fit and others who are very frail. Calendar age alone is a poor marker of the rate of ageing, often referred to as biological age.

Frailty is an age-related vulnerability that develops as a consequence of reduction in overall health.[66] There is no consensus on the precise measurement of frailty, but frailty has been shown to be a predictor of adverse health outcomes in older patients.[67] Although some studies show no effect of thyroid function variations on frailty measures, most prospective studies link higher thyroid function such as subclinical hyperthyroidism or per one unit increase in thyroid hormone concentrations to increased frailty and related parameters, such as decreased functional mobility and physical performance in older patients.[68–71] Two studies[72,73] have investigated the effect of thyroid function variations on gait speed and other gait domains (eg, tandem walk) in older people. In both studies slower gait speed was associated with higher thyroid function, defined either by a continous scale or as high-to-normal FT4 values. In their analysis, Bano and colleagues[73] showed that low and high TSH concentrations were associated with different gait domains, including changes in tandem walk, base of support and gait velocity.

Age-related macular degeneration is the most common cause of impaired vision in older people. In a

population-based cohort study with over 10 000 community-dwelling middle-aged and older people, higher concentrations of FT4 were associated with a higher risk of age-related macular degeneration.[74]

Treatment considerations in older patients

Several factors can influence treatment of thyroid disease in older patients including uncertainty in diagnosis, comorbidities, concomitant drug use, and changes in HPT axis set point. Regardless of age at diagnosis, clinical hypothyroidism should be treated with levothyroxine.[41,42,75] However, in older patients levothyroxine requirements are lower than in younger patients and the American Thyroid Association (ATA) recommends initiating lower doses of levothyroxine to avoid overtreatment and exogenous hyperthyroidism.[41] For the management of subclinical hypothyroidism, the European Thyroid Association (ETA) distinguishes between patients below and above 70 years of age with a more conservative therapy in older patients (eg, a wait and see strategy in older patients with mild subclinical hypothyroidism; figure 1).[42,75] The ETA recommends a starting dose of 25 µg of levothyroxine for the treatment of subclinical hypothyroidism in patients with ischaemic heart disease and older patients, in contrast with 50–100 µg of levothyroxine for the general population.[42]

Treatment with levothyroxine-liothyronine (LT4/LT3) combination therapy is recommended by the ATA only in the setting of a trial or by the ETA only in specific patient populations (ie, adherent and biochemically well controlled patients with persistent complaints on LT4 treatment). There are no recommendations for combination therapy specific to older patients, and not many trials that include this age group.[76–78]

The treatment of hyperthyroidism in older patients predominantly depends on its underlying cause. In the USA, in contrast with Europe or Latin America, radioactive iodine (RAI) therapy is preferred over antithyroid drugs for the treatment of Graves' disease. In some situations antithyroid drugs are considered a preferred treatment, for example in patients with a low life expectancy. RAI is also preferred for treatment of toxic adenoma or multinodular goitre in older patients, with surgery being contraindicated in those with an increased surgical risk. If RAI treatment is chosen in older patients and those with comorbid conditions, there is an increased risk for transient worsening of hyperthyroidism and preventive measures should be taken. These measures include pretreatment with beta-adrenergic blocking drugs and with methimazole. However, the risks associated with RAI in frail older patients compared with healthy older patients are unknown, making individual treatment choices in older patients challenging.

No trials are available to show the effects of treatment of subclinical hyperthyroidism on cardiovascular, musculoskeletal, or neurological outcomes in any age group. Based on the available observations, treatment for subclinical hyperthyroidism is indicated at any TSH concentration in patients older than 65 years of age, and treatment is similar to that of clinical hyperthyroidism.[79] The ETA provides a schematic overview of diagnosis and management of subclinical hyperthyroidism, with a distinction between patients above and below 65 years of age (figure 2).[79]

Guideline recommendations for management of subclinical hypothyroidism are based on observational studies including collaborative IPD meta-analyses, because large randomised controlled trials with hard clinical endpoints are scarce. A Cochrane review[80] of 11 randomised clinical trials included heterogeneous populations, treatment durations, and outcomes in 350 participants and showed that levothyroxine replacement therapy did not result in a significant difference in health-related quality of life and symptoms, compared with placebo or no treatment. There were no trials with a primary outcome of cardiovascular disease or mortality, but there was some evidence indicating that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function. The TRUST trial[81] included 752 older patients with persistent subclinical hypothyroidism and an average age of 74 years and median TSH of 5·75 mIU/L. The trial showed no benefit of treatment with levothyroxine on thyroid-specific quality of life, the primary endpoint of the trial. Furthermore, there was no difference in a range of secondary endpoints including daily functioning, overall quality of life, muscle strength, and cognition. However, the trial was underpowered to assess effects on cardiovascular disease. Specific subgroups such as those with higher TSH concentrations, high symptom burden, positive thyroid peroxidase antibodies, and the oldest patients (>80 years) were not assessed or underrepresented, so no definitive conclusions could be made for these subgroups. The indication of the TRUST trial that treatment with levothyroxine in older people with subclinical hypothyroidism provides no symptomatic benefits is in line with current recommendations[42,75] against routine T4 treatment in older patients with subclinical hypothyroidism, especially in those with mild hypothyroidism and low symptom burden. More research is required so that definitive answers can be obtained for specific subgroups such as those with high symptom burden, higher TSH concentrations, younger participants, or older participants. Carefully studied treatment trials in individual patients should also be considered. The reported struggle of the TRUST trial[81] to recruit and retain the targeted number of patients is typical for research in older patients. Only 7% of all randomised controlled trials specifically target older patients,[82] and the older patients who do participate typically do not represent the general older population that visits the doctor, because of the exclusion criteria of these trials.[83] In the absence of randomised controlled trials, observational studies may be a good alternative to provide individual treatment

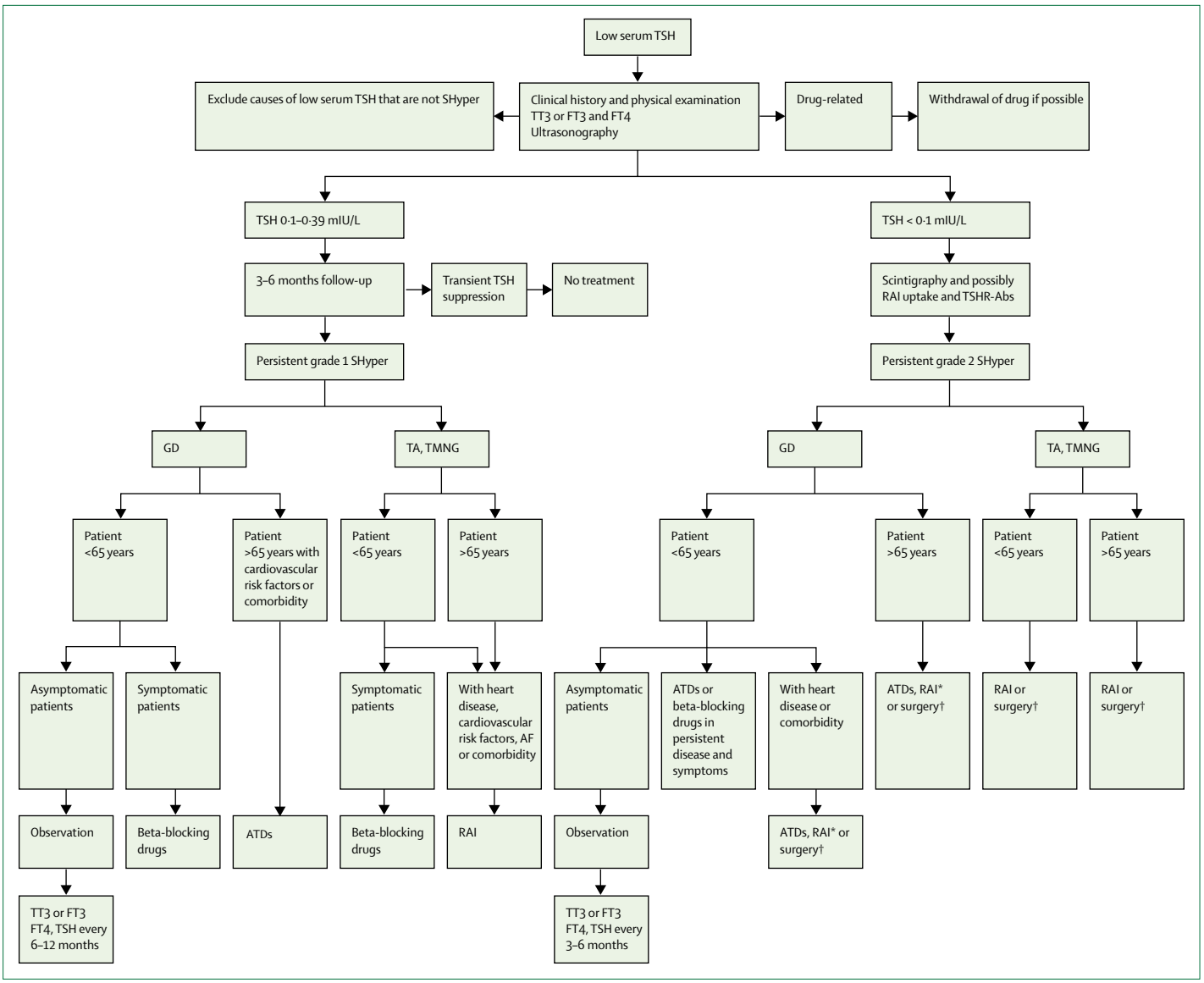

***Figure 2*: Treatment algorithm for subclinical hyperthyroidism**
This algorithm is based on the current European guideline.[79] TSH=thyroid-stimulating hormone. SHyper=subclinical hyperthyroidism. TT3=total triiodothyronine. FT3=free triiodothyronine. FT4=free thyroxine. RAI=radioactive iodine therapy. TSHR-Abs=TSH-receptor antibodies. Grade 1 SHyper=TSH concentrations 0·1–0·39 mIU/L. Grade 2 SHyper=TSH concentrations <0·1 mIU/L. GD=Graves' disease. TA=toxic adenoma. TMNG=toxic multinodular goitre. ATD=anti-thyroid drug. *RAI in patients with recurrences or if ATDs are not tolerated. †Surgery in patients with large goitre, symptoms of compression or thyroid malignancies. Reproduced from reference 79 by permission of the *European Thyroid Journal*.

recommendations. Although the evidence from the TRUST trial[81] provides evidence of no effect relevant to a large group of patients, there are still unanswered questions about the effects of levothyroxine on cardiovascular risk and about symptoms in older individuals with more severe subclinical hypothyroidism and those with symptomatology.

Directions for future research

Thyroid function changes with age and conversely, thyroid function can alter processes and outcomes in ageing. Determining the direction of causality is complex and challenging, but also crucial in the discussion concerning thyroid function reference ranges as well as diagnosis and treatment of thyroid disorders.

Information regarding changes in thyroid function in older patients over time is scarce and conflicting. Evidence concerning these changes in older individuals from different populations can also elucidate underlying pathophysiological pathways involving, for example, differences in individual iodine status and environmental issues. Collecting follow-up data on thyroid function earlier in life (ie, from 40 years of age or younger) can help to better distinguish between the causes of

Search strategy and selection criteria

We searched Embase, MEDLINE, and the Cochrane Library between Jan 1, 2000, and July 11, 2017, for articles published in or translated into English. The full literature search and search terms are provided in the appendix. We identified 3777 relevant articles in total, and mainly selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search and selected those we judged relevant, using the same inclusion and exclusion criteria as during our initial search. We supplemented the search with older records from our personal files. Review articles and guidelines are cited to provide additional details and references.

See Online for appendix

alterations in thyroid function due to temporal trends, changes over time, or ageing.

The references ranges of thyroid function are based on the 2·5–97·5 percentile of the distribution of FT4 and TSH serum measurements. The debate concerning the current definition of thyroid function tests is concentrated in particular around the older population. Several studies have shown that older people might have a tolerance to TSH concentrations beyond the upper reference range and others have associated subclinical hypothyroidism with a higher life expectancy.[52] In agreement with these findings, higher FT4 concentrations have been associated with adverse outcomes and decreased life expectancy within current reference ranges. Future studies investigating the effect of age-specific reference ranges on outcomes relevant to thyroid function, including cardiovascular, musculoskeletal, and neurological disease, and with a focus on both TSH and FT4 serum concentrations, could lead towards optimal health ranges for thyroid function in older people. These studies can serve to inform future trials investigating treatment thresholds for thyroid dysfunction in older adults.

Contributors

LC contributed to the literature search, outline, and writing of the manuscript. ARC and SPM contributed to the writing and critical revision of the manuscript. RPP contributed to the outline, writing, and critical revision of the manuscript.

Declaration of interests

RPP has received lecture fees from GoodLife Fertility BV and IBSA. All other authors declare no competing interests.

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