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REVIEW

Subclinical hypothyroidism and the development of heart failure: an overview of risk and effects on cardiac function

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Abstract

The prevalence of subclinical hypothyroidism (SCH) ranges from 5 to 15% of the general population. However, it remains controversial if SCH warrants life-long thyroxine replacement therapy. Patients with a thyroid-stimulating hormone (TSH) level > 10 mIU/L have a higher risk of developing heart failure with reduced ejection fraction as compared to subjects with normal thyroid function. However, abnormally high TSH levels could also be connected with an overall lower metabolic rate and better survival in elderly subjects. The potential mechanisms responsible for diastolic dysfunction of the left ventricle (LV) in SCH are connected with endothelial dysfunction and arterial stiffness, inflammatory state and are driven by TSH apoptosis-derived microparticles. The impact of SCH on LV systolic function is more controversial, and it is connected not only with cardiac remodelling but also with predisposition of patients with SCH to the conditions leading to heart failure. This review presents an overview of processes in the context of potential benefits of thyroxine supplementation therapy.

Keywords Subclinical hypothyroidism · Heart failure · Heart failure with preserved ejection fraction · L-thyroxine · Diastolic dysfunction

The scale and significance of subclinical hypothyroidism in the context of heart failure events and mortality

Subclinical hypothyroidism (SCH) can be identified by the detection of elevated thyroid-stimulating hormone (TSH) levels in serum in the presence of free thyroxine (T_4) and triiodothyronine (T_3) levels within the normal reference range. It is usually discovered on biochemical testing [1–3].

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The presence of SCH is usually associated with few or no definitive clinical signs or symptoms of thyroid dysfunction [1]. Autoimmunity is the commonest cause of SCH. About 2–5% of patients with SCH progress to clinically overt hypothyroidism each year; the rate of progression is higher in patients with thyroid autoantibodies and higher TSH levels [1, 2]. Although the prevalence of SCH may range from 5 to 15% in the general population [3], it remains controversial whether this condition warrants lifelong replacement T_4 therapy. In younger adults < 65 years, SCH is associated with an increased risk of coronary heart disease (CHD), heart failure (HF), and cerebrovascular disease [3, 4].

Subclinical hypothyroidism and incidence of heart failure

Several studies have addressed the effects of SCH on cardiovascular (CV) morbidity and mortality, however, a full understanding is still lacking. For example, the Healthy Aging and Body Composition study, a population-based analysis of 2730 men and women aged 70–79 years old, followed patients over 4 years investigating TSH levels and harmful CV effects. SCH was present in 12.4% of the subjects. Based on multivariate analyses, the study concluded

that patients with TSH from 7.0 to 9.9 mIU/L {hazard ratio (HR) 2.58 [95% confidence interval (95% CI) 1.19–5.6]} and TSH ≥ 10 mIU/L (HR 3.26, 95% CI 1.37–7.77) had up to a 3.26-fold higher risk for developing HF [5]. Similarly, the Cardiovascular Health Study performed echocardiography routinely for 6 years in a cohort of subjects to determine patients at risk for developing HF. It was found that patients with TSH > 10 mIU/L had higher risk of HF with reduced ejection fraction (HFrEF) as compared to the population with normal thyroid function [6]. Another study conducted by Rodondi et al. in over 55,000 individuals aged 18–100 years—3450 of whom had SCH (6.2%)—demonstrated a positive correlation between the degree of TSH elevations, CV event rates and mortality [7].

Gencer et al. [8] performed a pooled analysis of individual participant data using all available prospective cohorts with thyroid function tests and subsequent follow-up of HF events in 25,390 participants with 216,248 person-years of follow-up in the United States and Europe. A total of 2068 participants (8.1%) were found to have SCH. Risks of HF events were increased with higher TSH levels, particularly for TSH ≥ 10 mIU/L (Fig. 1) [8–11].

Definitions of selected parameters of cardiac function used in the text are presented in Table 1

Thyroid dysfunction in patients with HF

The circumstances in patients with established HF is altogether different than that from those in patients at risk of developing HF. Chen et al. performed a prospective follow-up study on the relationship between TSH levels and outcomes in patients with HF. A total of 5599 patients were followed at a health maintenance organisation and were assessed for cardiac-related hospitalisations and mortality. The median follow-up period was slightly over 14 months. From their results it became apparent that both a high TSH level and a low TSH level were associated with an increased mortality rate. Patients were divided into quartiles of TSH level, and the mortality in the highest quartile was 36% higher than that in the second quartile. Subjects with TSH > 10 mIU/L had a more than twofold increase in mortality [12]. Finally, a recent meta-analysis of prospective cohort studies has shown that SCH is associated with an increased risk of CHD-related events, CHD mortality and HF events, especially in individuals with TSH levels ≥ 10.0 mIU/L [13, 14].

In contrast to the aforementioned findings, investigators from the Leiden 85-plus study reported data from a prospective, observational population-based study in 599 individuals aged 85 through 89 years who were followed for a mean of

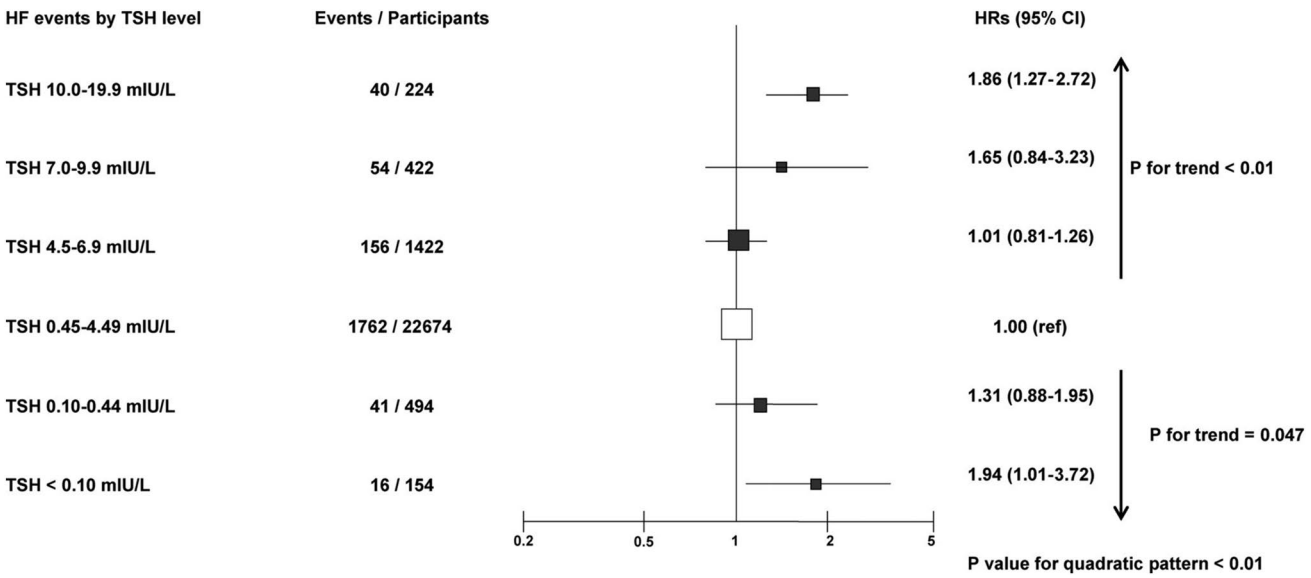

Fig. 1 Forest plots of Heart Failure (HF) events in Subclinical Hypothyroidism vs. Euthyroidism adapted from Gencer B, Collet TH, Virgini V, et al. Thyroid Studies C. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation 2012;126:1040–1049 [8]. *CI* confidence interval, *HR* hazard ratio age- and gender-adjusted HRs and their 95% CI are represented by squares. Squares to the right of the solid lines indicate increased risk of HF events

Table 1 Definitions of selected parameters of cardiac function used in text

Parameter of cardiac function	Definition	Relevant references
Augmentation index (AI)	It is determined from either a directly measured or a derived central arterial pressure waveform proposed as a measure of aortic stiffness and wave reflection, AI is the percentage of central pulse pressure attributable to the secondary systolic pressure rise produced by the overlap of the forward and reflected pressure waves	[32, 36]
Pulse wave velocity (PWV)	It is the velocity at which the arterial pulse propagates through the circulatory system. PWV is used clinically as a measure of arterial stiffness. It is easy to measure invasively and non-invasively in humans, it is highly reproducible and has a strong correlation with cardiovascular events and all-cause mortality	[32, 34]
Isovolumetric relaxation time (IVRT)	It is an interval in the cardiac cycle, from the aortic component of the second heart sound, that is, closure of the aortic valve, to the onset of filling by opening of the mitral valve	[20, 21, 28, 29]
Pulsed wave tissue Doppler imaging (PWTDI)	This technique uses the Doppler principle to assess the ventricular wall motion velocity by positioning the sample volume within the myocardium	[20, 21]
E/*A* ratio	The *E*/*A* ratio represents the ratio of peak velocity blood flow in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave) assessed by PW Doppler	[17]
e' a'	The *e*′ (*e* prime) represents the early diastolic filling velocity and the *a*′ (*a* prime) the late diastolic filling velocity using tissue Doppler of the mitral annulus	[17, 35]
Myocardial precontraction time (PCTm)	It is the time from the onset of ECG QRS complex to the beginning of the mitral annular peak systolic velocity	[20]
Myocardial contraction time (CTm)	It is the time from the beginning to the end of the mitral annular peak systolic velocity	[20]
Preejectional period (PEP)	It is a delay from the Q wave of the QRS complex to the aortic valve opening; PEP is the interval from the onset of ventricular depolarisation to the beginning of aortic ejection	[20, 55]
Left ventricular ejection time (LVET)	It represents the interval from beginning to termination of aortic flow	[20]
Myocardial performance index (Tei index)	It is an index that incorporates both systolic and diastolic time intervals in expressing global systolic and diastolic ventricular function. Systolic dysfunction prolongs preejection (isovolumetric contraction time) and shortens the LVET. Both systolic and diastolic dysfunction result in abnormality in myocardial relaxation which prolongs the IVRT	[54, 55, 58]
Cardio-ankle vascular index (CAVI)	CAVI reflects the stiffness of the aorta, femoral artery, tibial artery and involves measurement of brachial, ankle PWV and blood pressure. It is obtained by recording the distance from the level of the aortic valve to the measuring point (for example the ankle) and the time delay between the closing of the aortic valve to the detected change in arterial pressure wave at the set point	[35]

3.7 years. Controversially, increasing levels of TSH were associated with a lower mortality rate that remained after adjustments were made for baseline disability and health status. The abnormally high TSH levels could be linked to a lower metabolic rate and perhaps to caloric restriction as a result of this state [15]. However, such observational results should be interpreted with caution as other alterations in the oldest age group are also—and counterintuitively—associated with better survival, such as high blood pressure and high cholesterol.

In patients admitted for acute HF, Hayashi et al. [14] have recently shown that SCH is an independent predictor of adverse CV outcomes, suggesting a possible interaction between thyroid dysfunction and the pathophysiology of this state [14]. In light of the foregoing findings, it is somewhat disappointing to learn that the 2016 European Society of Cardiology (ESC) guidelines for the management of HF mention only that both hypothyroidism and hyperthyroidism may precipitate acute HF. Accordingly, TSH should be assessed in all newly diagnosed patients with acute HF. The impact of different TSH levels is not discussed in the HF guideline [16].

Subclinical hypothyroidism and diastolic dysfunction

Previous studies have documented the role of diastolic dysfunction in the development and progression of HF with preserved ejection fraction (HFpEF) [17–19]. Although there is no clear evidence that SCH causes clinical heart disease [16], changes in thyroid status in SCH are associated with changes in several cardiac parameters manifested by left ventricular dysfunction at rest and systolic dysfunction on effort. Vitale et al. [20] conducted a study with 40 women: 20 healthy and 20 with established SCH (mean TSH > 10 mIU/L over 6 months). They underwent standard Doppler and pulsed wave tissue Doppler imaging (PWTDI). Standard Doppler showed an increase in LV preejection period (PEP), preejection period/LV ejection time ratio (PEP/LVET) and isovolumetric relaxation time (IVRT) in SCH ($r = 0.35$; $p < 0.05$; Table 1). By PWTDI analysis, the adjusted myocardial precontraction time/myocardial contraction time ratio (PCTm/CTm) was positively associated with TSH ($r = 0.32$; $p < 0.05$), as well as the adjusted myocardial relaxation time (RTm) at the level of the posterior septum ($r = 0.40$; $p < 0.01$). In the whole population, IVRT, PCTm, and RTm were negatively related to FT4 (Table 1) [20]. Similarly Zoncu et al. demonstrated in a study with 32 subjects with classical Hashimoto's thyroiditis (69% with TSH > 3 mU/mL) that PWTDI indices were delayed in diastolic relaxation and decreased in the compliance to the ventricular filling [21].

Case–control studies found patients with SCH to have prolonged IVRT, increased peak atrial filling velocity (A wave), and a diminished ratio of peak velocity flow in early diastole (E wave) to peak velocity flow in late diastole caused by atrial contraction (E/A ratio) [17]. In the aforementioned Cardiovascular Health Study [6] 3044 adults with ≥ 65 years underwent a mean 12-year-follow-up and changes in the cardiac function over 5 years. Participants with TSH ≥ 10.0–19.9 mIU/L who were untreated by thyroxine replacement had a greater incidence of HF events compared to euthyroid participants (41.7 vs. 22.9/1000 person-years, $p = 0.01$), but rates were similar for those with TSH between 4.5 and 9.9 mIU/L. Echocardiography was obtained on 70.6% of participants after 5 years; In the more pronounced SCH subgroup (TSH ≥ 10 mIU/L) there was a larger increase in LV mass (+ 21 vs. +4 g, $p = 0.04$). Peak E velocity decreased more than in euthyroid participants (− 0.10 vs. −0.01 m/s, $p = 0.005$), which might be related to the gain in LV mass over time and progressive impairment of LV relaxation [22, 23]. The higher early diastolic filling velocity reflects increased left atrial pressure (LAP) and diastolic dysfunction. Nonetheless CV abnormalities have been shown to regress with L-thyroxine therapy [24–26]. Other studies have controversially shown that cardiac structure and function remain overall normal in SCH [26].

Pathogenical mechanisms linking subclinical hypothyroidism to diastolic dysfunction

Endothelial dysfunction and arterial stiffness

Central aortic stiffness is augmented in many patients with HF and some researchers have assumed a relationship of arterial stiffness and early diastolic dysfunction in middle-aged and elderly populations [27, 28]. Differences in central aortic stiffness are also present in HFpEF patients in the absence of other parameters of diastolic function, as assessed by PWTDI, and correlate with LV mass and B-type natriuretic (BNP) levels, highlighting the potential contribution of abnormal pulsatile load and arterio-ventricular coupling (interaction of arterial stiffness, systolic and diastolic function) to the development of HF. However, this mechanism is not yet completely understood [28, 29]. Increased arterial stiffness is involved in the development of diastolic dysfunction via impairment of coronary blood supply as a consequence of a reduced diastolic blood pressure, induction of cardiac hypertrophy or, incremented cardiac stiffening [29]. Moreover, aortic stiffness leads to an increase in afterload, which itself strengthens the pulse pressure, resulting in higher oxygen consumption. A reduction in diastolic blood pressure leads as well to diminished myocardial perfusion. In summary, diastolic relaxation is deranged in case of elevated afterload [30, 31].

The decline in global endothelial function is associated with parameters of arterial stiffness—increased aortic stiffness assessed via pulsed wave velocity (PWV) and augmentation index (AI) (Table 1) [32]. Stiffness of large arteries and central haemodynamics, on the other hand, are influenced by endothelial function and support findings describing the importance of nitric oxide (NO) in the regulation of large artery stiffness in vivo [32]. SCH may be directly associated with endothelial dysfunction and impaired coronary flow reserve through specific molecular pathways in endothelial cells, by affecting NO production and by facilitating increased degradation of vasodepressor intermediates [33]. Several studies have demonstrated cellular, subcellular and intercellular transformation in patients with HFpEF, for instance, cytokine-mediated dysfunction of myocyte strain and defects of myofibroblasts with resulting left ventricular fibrosis. However, the disturbed arterio-ventricular coupling is one of the main factors for developing left ventricular failure in patients with HFpEF [31]. In addition, reduced cardiac preload has been shown via cardiac magnetic resonance imaging (MRI) in patients with SCH together with increased

afterload [2]. After a period of T_4 therapy in these patients, the haemodynamic alterations were well reversible.

Another parameter for the assessment of arterial stiffening and a predictor for the presence of CHD is brachial-ankle PWV. Significantly elevated values of brachial-ankle PWV have interestingly been reported in patients with SCH [34]. Masaki et al. conducted a cross-sectional study of 83 patients with untreated SCH and compared them with 83 randomly selected controls from health check-ups to assess the relationship of thyroid hormone level to cardio-ankle vascular index (CAVI) (Table 1) and left ventricular diastolic function. When compared with the control group, patients with SCH had significantly higher values of N-terminal pro-BNP (NT-proBNP), C-reactive protein (CRP), and CAVI as well as lower e' values. In the SCH group, CAVI was significantly associated with NT-proBNP, CRP and e'. These findings suggest that SCH may be a risk factor for CV events related to arterial stiffening and left ventricular diastolic dysfunction [35]. Owen et al. revealed that arterial stiffness is increased in SCH and improves with L-thyroxine therapy, which may be beneficial, whereas myocardial functional reserve was similar to controls and remained unaltered after treatment (Fig. 2) [36].

Apoptotic-derived extracellular microparticles

The pathogenesis of diastolic dysfunction might be influenced by TSH stimuli for apoptotic-derived microparticles. In this context, it is important to understand extracellular microparticles (EMPs). EMPs are microvesicles with sizes ranging between 50 and 1000 nm released from plasma membranes of different cell types, such as endothelial cells, mononuclear cells or platelets. Such EMPs are released upon specific (e.g. cytokine stimulation, apoptotic agents, mononuclear cooperation, coagulation) and non-specific (shear stress) stimuli [39]. EMPs transport microribonucleic acid (miRNA), active molecules, hormones, peptides, regulator proteins and other substances, thereby mediating cell-to-cell cross-talk [37]. Their role is not entirely clear, but they seem to take part in endothelial reparation, tissue injury, and vascular remodelling [38]. The different patterns of circulating EMPs in CV diseases including HF suggest that impaired EMP phenotypes are potentially available for risk stratification in patients with CV and metabolic disease [39, 40]. In this context, circulating EMPs may function as novel biological markers for endothelial injury, vascular tone disorders, and vascular aging, which may demonstrate the impact of SCH in CV disease progression. However, it remains controversial whether or not a causal role of EMP patterns in patients with HF with SCH exists [41]. An example of this controversy is that it is still unknown if circulating EMPs found in peripheral blood cause injury to the endothelium and worsening HF and whether they are the result of disease progression in response to endothelial dysfunction and vascular disintegrity [42]. The results of the study of Berezin et al. suggest that SCH in patients with HF might be associated with an impaired release pattern of circulating EMPs with a predominantly increased number of apoptotic-derived microparticles [43]. In cohort of 388 patients with HF, 53 of whom had SCH, the presence of SCH was associated with an impaired pattern of circulating EMPs with predominantly increased number of apoptotic-derived microparticles [44].

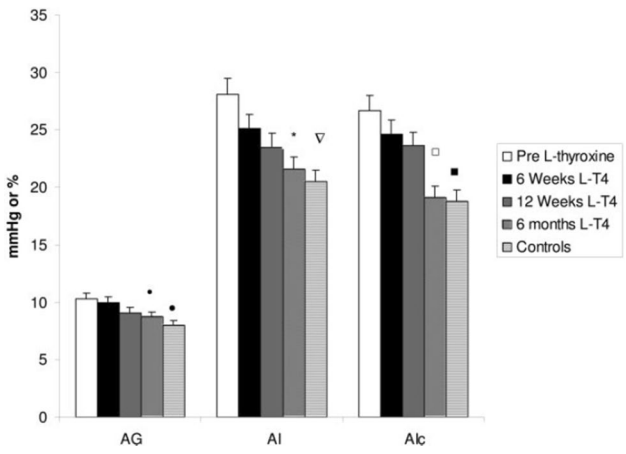

Fig. 2 Indices of central arterial stiffness in SCH patients before and after 6 months of L-thyroxine [36]. *AG* augmentation gradient (mm Hg), *AI* augmentation index (percent), *AIc* corrected augmentation index (percent). Significance levels: $*p<0.0001$, before treatment, compared with post treatment for AI; $\bullet p<0.05$, pre-treatment, compared with post treatment for AG; $\Lambda p<0.001$, pre-treatment, compared with controls, for AI; $\square p<0.001$, pre-treatment, compared with post treatment for AIc; $\blacksquare p<0.002$, pre-treatment, compared with controls for AIc

Systemic inflammation

Apart from EMPs, some evidence points towards a strong involvement of systemic inflammation associated with diastolic dysfunction, which may also impact the remodelling process [45, 46]. Gupta et al. found TSH levels to be positively correlated with inflammatory markers such as CRP, interleukin-6 (IL-6), and erythrocyte sedimentation rate (ESR) in patients with SCH. They were significantly higher in SCH, subsequently increasing with disease progression and in the absence of treatment [47]. These findings (elevated levels of CRP and IL-6) are in line with those reported by Vaya et al. and Taddai et al. [48, 49]. The interaction between SCH and LV diastolic dysfunction are presented in Fig. 3.

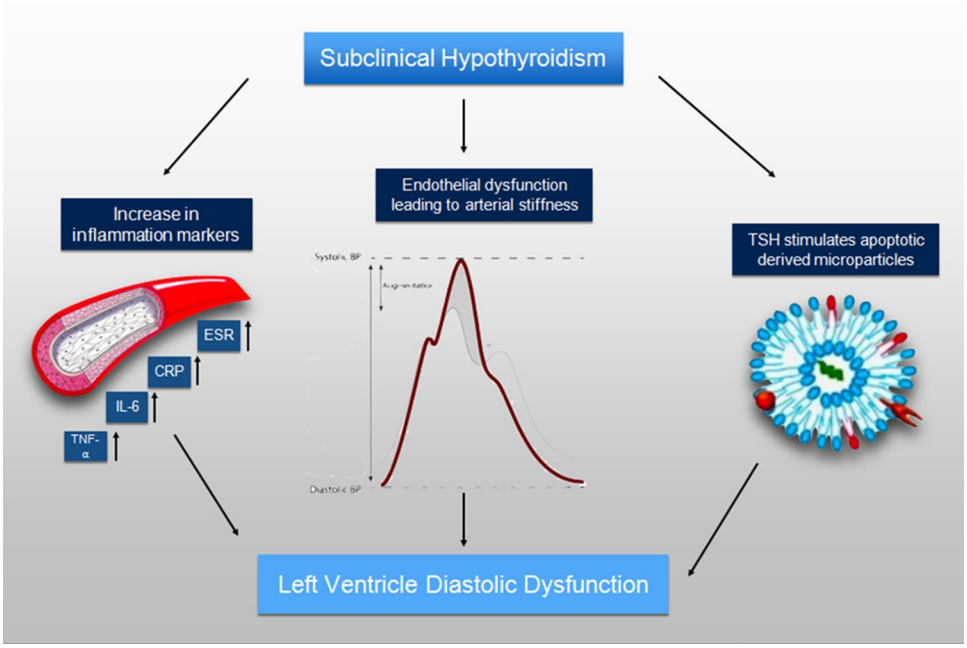

Fig. 3 The interaction between subclinical hypothyroidism and left ventricular diastolic dysfunction. *TNF-α* tumour necrosis factor α, *IL-6* interleukin 6, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

The impact of subclinical hypothyroidism on systolic function

The impact of SCH on left ventricular systolic function is more contentious than that on diastolic function. As discussed earlier, SCH can represent a risk factor for the progression of chronic HF. SCH may induce cardiac remodelling by influencing the expression of genes involved in calcium handling and contractile properties of myocardiocytes [50] but also through tissue changes (e.g. collagen alteration, dehydration, myocardial fibre orientation or capillary distribution) [25, 51].

SCH may also favour the blossoming of substrate conditions, such as dyslipidaemia and atherogenesis, which implicate in the progression of chronic HF. Examining the prevalence of CHD in subjects with and without SCH, Walsh et al. found a higher risk of CHD in patients with SCH. This ratio prevailed even after adjustment for standard CV risk factors, sex and age. Since CHD is arguably one of the most common causes of HF, the potential contribution of thyroid abnormality to the development of HF is evident [52]. Pesic et al. examined 120 patient, 60 with SCH and 60 healthy individuals to assess the metabolic syndrome components. The following indices were statistically significantly higher in SCH subjects: body mass index, diastolic blood pressure, total cholesterol, triglycerides and basal insulin level [53].

Few studies have investigated the effects of SCH on left ventricular systolic function. Ilic et al. reported that the LV mass index of patients with SCH was elevated before and also after replacement therapy as compared to controls. Besides, global LV function estimated by the myocardial performance index (Tei index) (Table 1) was impaired and the LV systolic function was lessened in SCH patients as compared to controls. Additionally, SCH participants had enlarged right ventricular (RV) wall thickness and impaired RV diastolic and global function [54]. Some researchers presented results indicating that LV ejection fraction was unchanged among SCH patients [55–58].

Impaired LV diastolic function at rest may be an important cause of systolic dysfunction on effort in patients with SCH. The increase in heart rate in response to exercise reduces LV diastolic filling time [59]. Under physiologic conditions, this effect is counterbalanced by an improvement in diastolic function. In this context, a slowed rate of LV relaxation in patients with SCH could critically undermine ventricular filling during exercise and together with altered vascular reactivity yield LV systolic dysfunction [59]. The first assessment of cardiac function on effort in patients with SCH has been performed by Bell et al. using radionuclide ventriculography. They demonstrated that the restoration of euthyroidism by L-thyroxine administration—compared to pre-treatment values—induced a small but significant rise in the peak exercise LV ejection fraction, although there was no change at rest or during moderate effort [60]. Kahaly et al. revealed that the oxygen pulse (oxygen uptake per heart beat), an index assumed to represent LV stroke volume, was also reduced both at the anaerobic threshold and at maximal exercise, and the work rate was diminished at the anaerobic threshold in untreated patients [61].

Subclinical hypothyroidism as a therapeutic target

As discussed above, thyroid hormone dysfunction can result in altered ventricular contractility and relaxation dynamics as well as compromised cardiac function. These considerations have important clinical implications in that thyroid dysfunction represents one of the few potentially reversible causes of HF [55, 62]. Unfortunately, there is a paucity of evidence on the beneficial effects of thyroxine hormone replacement on CV mortality outcomes in patients with SCH [63]. Also, the clinical relevance of measuring and treating supra-normal TSH levels in newly diagnosed patients with HFpEF requires further study [41].

The available evidence suggests that several cardiac function parameters are normalised in patients treated for SCH. L-thyroxine in SCH decreased the ratio between PEP and LV ejection time in 46 adults [55] and improved cardiac preload and contractility in 30 women [2]. Nevertheless, these studies are limited by their small sample size, short duration, non-standardised definitions of SCH or echo measurements [11]. The effects of thyroid hormone supplementation was further prospectively evaluated in a double-blind, randomised, placebo-controlled, parallel-group trial in 737 subjects who were at least 65 years of age with SCH in the TRUST trial (Thyroid Hormone Replacement for Subclinical Hypo-Thyroidism) [64]. In this study, SCH was defined as having TSH levels between 4.5 and 20 mIU/L, with free T_4 levels still within the normal range. A total of 368 patients were assigned to receive L-thyroxine and 369 patients to receive placebo. The authors found no difference in the mean change at 1 year in the Hypothyroid Symptoms score and the Tiredness score between the L-thyroxine and the control group. The incidence of serious adverse events of special interest (atrial fibrillation, HF, fracture, or new diagnosis of osteoporosis) was similar in the two groups. L-thyroxine provided no apparent benefit in older persons with SCH. It is worth to notice that observational studies show that TSH tends to increase with age, which seems to be a physiological process and a marker of advancing age rather than a pathological development [64, 65]. There might be a danger of SCH overdiagnosis, especially in the elderly, but age-based cut-off points have not yet been standardised. In the context of the TRUST trial it is worth to see the potential outcomes of the use of thyroxine to treat SCH in younger population [65–67]. For that matter a large observational study of the UK General Practice Research Database has corroborated that L-thyroxine may minimise the risk of CHD in younger patients (< 70 years) [3].

Conclusion

Patients with SCH are presently often classified into 2 groups: those with mild SCH in whom TSH is mildly increased (TSH 4.5–9.9 mIU/L) and those with a more severe dysfunction when TSH is ≥ 10 mIU/L. A slightly increased serum TSH might not always reflect mild thyroid hormone deficiency but rather different reference values at different ages [68]. Thus, cut-off limits for age and age-adjusted serum TSH levels should be accounted for during L-thyroxine replacement therapy [69].

In 2005, a consensus panel from the American Association of Clinical Endocrinologists, the American Thyroid Association and the Endocrine Society recommended against replacing thyroid hormones if TSH is < 10 mIU/L but that treatment was reasonable if TSH is > 10 mIU/L [70]. Cooper and Biondi recommend on the other hand to treat patients with mild SCH, but only in those < 75 years [71]. Otherwise treatment should be individualised [72]. It has also not been determined which patients are likely to progress to overt hypothyroidism.

Thyroid dysfunction emerges as a comorbidity of HF. It is noteworthy that the current recommendations stem from endocrinological, yet not cardiological guidelines. We encourage that a subset of SCH patients, in which the treatment may warrant overall benefit, should be contemplated, foremost those with hypertension, hyperlipidaemia, atherosclerosis, arterial stiffness, CHD and early or established diastolic dysfunction.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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