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REVIEW

Clinical Update

Subclinical thyroid dysfunction and cardiovascular diseases: 2016 update

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Subclinical thyroid dysfunction comprises subclinical hypothyroidism (SHypo), defined as elevated thyroid-stimulating hormone (TSH) by normal free thyroxine (FT4), and subclinical hyperthyroidism (SHyper) with decreased or undetectable TSH and normal FT4. Up to 10% of the elderly have SHypo, which is usually asymptomatic. Individual participant data (IPD) analyses of prospective cohort studies from the international Thyroid Studies Collaboration show that SHypo is associated with increased coronary heart disease (CHD) mortality [hazard ratio (HR) 1,58 for TSH ≥ 10 mIU/L, 95% CI 1.10–2.27), as well as increased risk of stroke, and heart failure (HF) for both higher and lower TSH. Small studies found that SHypo affects carotid intima media thickness (CIMT), diastolic function, peripheral vascular resistance, endothelial function, and lipid profile. SHyper is associated with increased risk of atrial fibrillation (AF) (HR 1.68, 95% CI 1.16–2.43) and CHD events (HR 1.21, 95% CI 0.99–1.46). The TSH threshold for initiating treatment is unclear. In the absence of large randomized controlled trials, the best evidence suggests SHypo therapy should be started at TSH ≥ 10 mIU/L, and SHyper therapy at TSH < 0.1 mIU/L. Recommendations on screening are discordant, but most guidelines advocate that thyroid function should be checked in those at risk for hypothyroidism, those over 60, and those with known CHD and HF. This review updates current evidence on the association between thyroid dysfunction and cardiovascular disease, as well as on screening and treatment of subclinical thyroid dysfunction.

Keywords Subclinical hypothyroidism • Subclinical hyperthyroidism • TSH • Cardiovascular diseases • Screening • Treatment

Clinical and epidemiological relevance of subclinical thyroid dysfunction

Subclinical thyroid dysfunction comprises subclinical hypothyroidism (SHypo) and subclinical hyperthyroidism (SHyper). SHypo is defined as thyroid-stimulating-hormone (TSH) above the normal range, with normal free thyroxine (FT4).[1] SHypo can reach up to 10%, and is most prevalent among elderly women.[2] Recent data show that SHypo is associated with coronary heart disease (CHD),[3–7] heart failure (HF),[8] and stroke.[9] Endogenous SHyper is defined as low or undetectable TSH, with FT4 and free triiodothyronine (FT3) within the reference range. SHyper is associated with increased CHD events, CHD mortality, and incident atrial fibrillation (AF).[10] In the National Health and Nutrition Examination Survey III, 0.7% of participants had TSH < 0.1 mIU/L and 1.8% < 0.4 mIU/L.[11] The prevalence of SHyper depends on age, sex and iodine intake.[12] Exogenous SHyper is caused by thyroid hormone replacement in up to 20% of treated patients. A retrospective cohort study on levothyroxine prescription among 52 298 participants showed that after 5 years of treatment, 5.8% of participants had TSH < 0.1 mIU/L.[13]

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Biochemical definition of subclinical thyroid dysfunction and variations according to population characteristics

Third generation TSH chemiluminometric assay is widely used and allows to detect changes of ~0.01 mIU/L. TSH within the hyperthyroid range can now reliably be distinguished from euthyroid, although there is still debate over the lower limit of the TSH reference range.[14] For SHypo, controversy remains about the TSH range and upper limit.[15–17] Most guidelines set an upper limit of 4.4–5.0 mIU/L, but the majority of euthyroid individuals fall between 0.4 and 2.5 mIU/L, depending on their iodine intake.[2,18] Observational studies show that TSH tends to increase with age,[19,20] which seems to be a physiological process and a marker of frailty rather than a pathological development. There might be a danger of SHypo overdiagnosis, especially in the elderly, but age-based cut-off points have not yet been standardized.[21] The underlying mechanisms leading to overt hypothyroidism, characterized by TSH above and FT4 below the reference range, are still not clear, though, one study described the average yearly progression rate as ranging from 2 to 6%, depending on the presence of antithyroid peroxidase antibodies and on initial TSH.[22]

General pathophysiological aspects

Each individual probably has a specific, genetically determined set point for the hypothalamic-pituitary-thyroid axis.[23–25] A Danish twin study found heritability accounted for 64% of TSH variation (95% CI: 57–70%), 65% of FT4 variation (95% CI: 58–71%), and 64% of FT3 variation (95% CI: 57–70%).[25] FT4 plays the most important role in regulating TSH secretion (*Figure 1*). Minimal changes in FT4 have a strong effect on TSH secretion,[26] but the earlier description of the regulating mechanism as a log-linear relationship between TSH and FT4 has been challenged. Mathematical models show the relationship is better represented by two overlapping sigmoid curves, where TSH is expected to be higher for men and the elderly.[27] Symptoms of thyroid dysfunction are sometimes nonspecific: fatigue and depression are frequent, as are dyslipidaemia, weight gain, constipation. More extreme symptoms are pericardial effusion and myxoedema. Subjects with SHypo rarely report the full cluster of symptoms, but frequently report symptoms like tiredness,[28] cramps, weakness, and myalgia.[29] Clinical manifestation of SHyper is less pronounced than it is for overt hyperthyroidism (characterized by low or undetectable TSH and FT3/FT4 above the reference range). For SHyper, symptoms may be absent or similar to overt hyperthyroidism[12]: increased metabolic basal rate and thermogenesis (systemic symptoms),[12] sinus tachycardia, AF, congestive HF, and peripheral vasodilation with ankle oedema (cardiac symptoms).[30,31]

Thyroid dysfunction and the heart: pathophysiological mechanisms

Peripheral deiodinases convert thyroxine to triiodothyronine, the active form of thyroid hormones. Within the cell, triiodothyronine is a transcriptional and extranuclear modulating factor that stimulates activity of cardiac myocytes and vascular smooth muscle cells. Triiodothyronine regulates the expression of structural and functional proteins, like calcium-activated ATPase and phospholamban, at DNA level.[32] Triiodothyronine also regulates the intracellular calcium concentration, and determines systolic contractile function and diastolic relaxation. Triiodothyronine interacts directly with sodium, potassium, and calcium channels, modulating ionic exchange between intra- and extracellular compartments, and improving cardiac inotropy and chronotropy[32,33] (*Figure 2*).

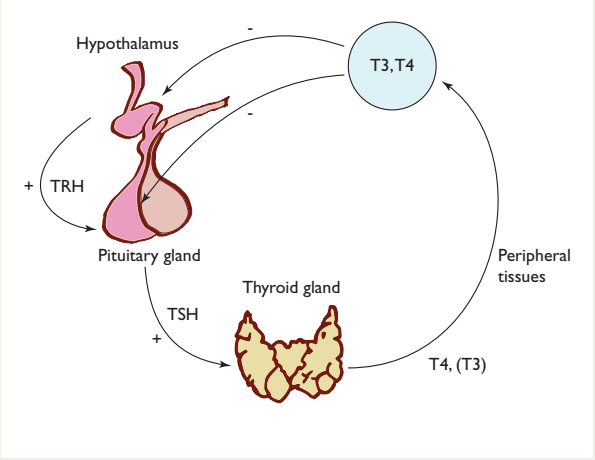

Figure 1 Simplified illustration of thyroid hormones homeostasis. TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine.

Overt hypothyroidism can cause cardiac anomalies, including (i) rhythmic disorders like bradycardia and atrioventricular block[30]; (ii) myocardial abnormalities like impaired systolic function, increased left ventricular (LV) diastolic filling, diastolic dysfunction with impaired cardiac relaxation, pulmonary hypertension, atrial stiffness, pericardial effusion; and, (iii) vascular disturbances like endothelial dysfunction and arterial hypertension[33] (*Figure 3*). LV stroke volume can be decreased by bradycardia, increased diastolic pressure, atrial stiffness, and poor contractility, which can also aggravate HF.[32,34] LV ejection fraction is the most widely reported outcome in studies on HF and CHD for risk stratification and medical decision.[35] Global heart function is the result of the interaction of myocardial contractility, preload (end-diastolic volume), heart rate, and afterload. Because half of patients with HF events have preserved ejection fraction, guidelines recommend to use additional endpoints of diastolic function and LV pressing filling, such as transmitral inflow patterns (E-, A-wave, and E/A), pulsed TVI-derived early diastolic velocity of the mitral annulus (E/e' ratio) and left atrial volume.[35]

In SHypo anomalies are more common at higher TSH and among the elderly.[36] It is specifically associated with diastolic dysfunction. Case-control studies found patients with SHypo have prolonged Isovolumic Relaxation Time (IRT), increased A wave, and diminished E/A ratio.[36] In the Cardiovascular Health Study, the 3044 patients ≥ 65 years with TSH ≥ 10 mIU/L had higher baseline peak E velocity (0.80 m/s) than those with normal TSH (0.72 m/s, $P = 0.002$).[37] In addition, each 0.1 m/s increase in E wave velocity was associated with

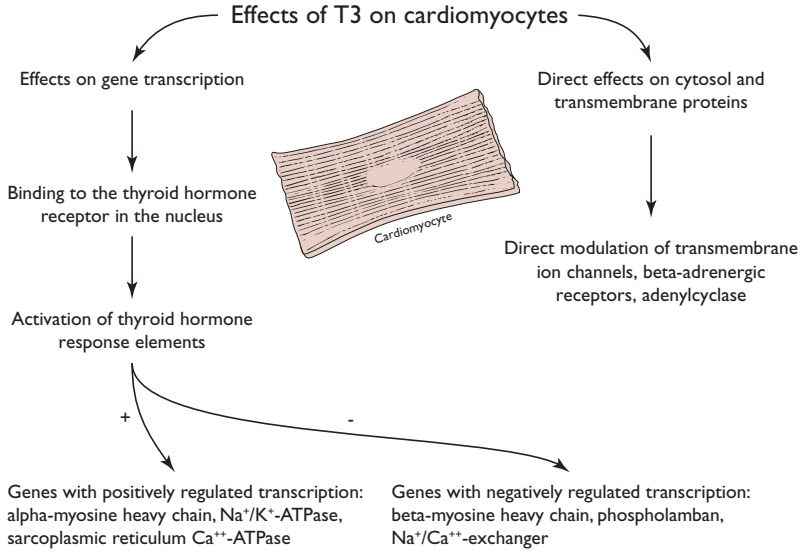

Figure 2 Effect of T3 on the cardiomyocytes. T3, triiodothyronine.

higher risk of HF events (HR 1.14, 95% CI 1.08–1.18, $P < 0.001$), especially with TSH ≥ 10 mIU/L (HR 1.45, 95% CI 1.20–1.76).[37]

Overt hyperthyroidism affects the cardiac pacemaker function and contractility.[31,38] SHyper, on the other hand, is associated with more premature atrial and ventricular beats, higher mean heart rate over 24 h,[12] and increased risk of AF.[10] Cardiac changes in hyperthyroidism can be explained by the positive inotropic, chronotropic, and lusitropic effects of triiodothyronine that might be associated with higher cardiovascular morbidity and mortality.[12] The effects of thyroid hormones on the heart in hyperthyroidism mimic a hyper-adrenergic state although there is no evidence that thyroid hormones affect the responsiveness of the heart to catecholamines (*Figure 3*). Some β-adrenergic elements in cardiomyocytes like the β1-adrenergic receptors and the adenylate cyclase are regulated by the thyroid hormones.[31]

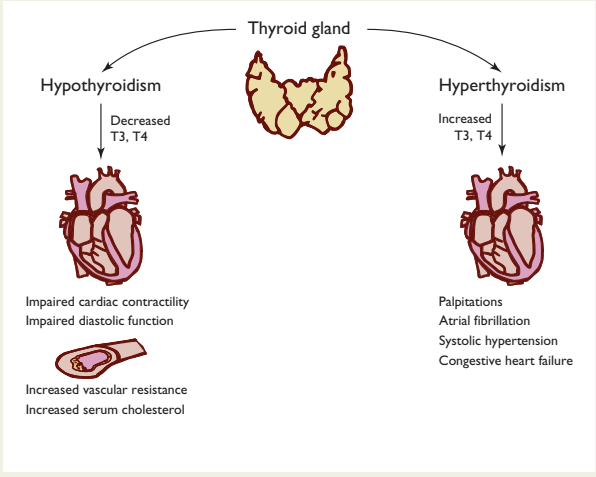

Figure 3 Some mechanisms by which thyroid dysfunction affects the cardiovascular system.

Subclinical thyroid dysfunction and surrogate cardiovascular markers

Carotid Intima Media Thickness (CIMT) is a surrogate cardiovascular endpoint[39–41] associated with both SHyper and SHypo.[12] CIMT may be an independent predictor for cardiovascular events, although its usefulness for classifying risk is still unclear.[42] A meta-analysis found that each 0.10 mm IMT increase corresponded to an increased RR for myocardial infarction of 1.15 (95% CI 1.12–1.17) and for stroke of 1.18 (95% CI 1.16–1.21).[43]

In a case-control study, CIMT was significantly higher among the 36 patients with SHypo (0.66 mm ± 0.10) than the 32 controls (0.57 mm ± 0.08).[39] In a double-blind cross-over trial, 100 patients (mean age 53.8 years) with no prior thyroid dysfunction were randomized to 100 μg levothyroxine or placebo once a day for 12 weeks. After treatment, total lipoprotein decreased from 231.6 to 220 mg/dL; low-density lipoprotein cholesterol decreased from 142.9 to 131.3 mg/dL. Brachial artery flow-mediated dilatation, a marker of endothelial function, improved after treatment, probably because of increased FT4.[28] Changes in coagulation and fibrinolytic cascade are related to SHypo, and might explain increased risk of stroke in those under 65 years observed in SHypo.[9]

SHyper, on the other hand, might be accompanied by changes in the coagulation cascade that increase the risk of thrombosis, although it is unclear if this risk is clinically relevant.[12]

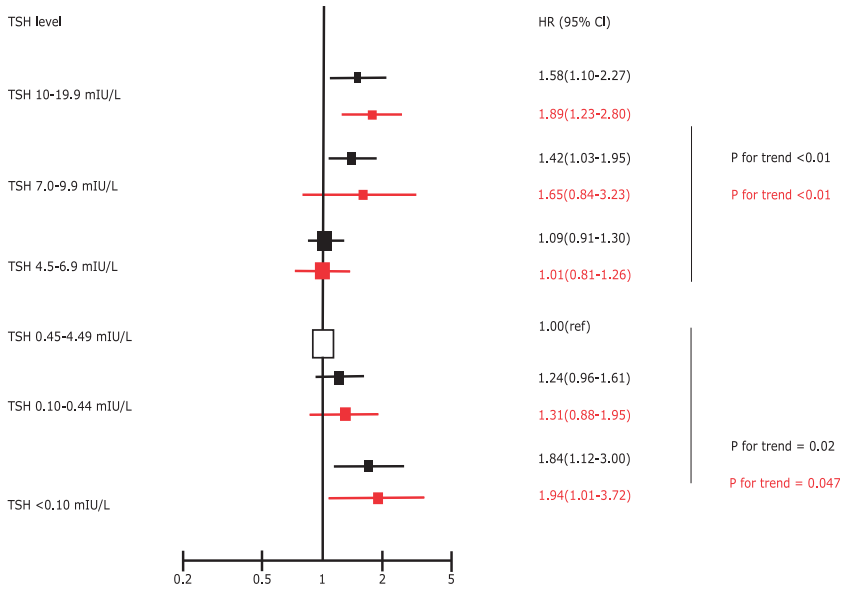

Figure 4 HRs for Coronary Heart Disease Mortality (black) and Heart Failure Event (red) based on TSH Levels (adapted from Refs. 4 and 8). Age- and sex-adjusted HRs and their 95% CIs, presented by squares (reproduced with permission from Ref. 49).

The international thyroid studies collaboration

To better assess cardiovascular disease risk in subclinical thyroid dysfunction, we setup the 'Thyroid Studies Collaboration'', an international consortium that contributed individual participant data (IPD) from 18 prospective cohorts, including 73 000 participants across four continents.[4,8–10,44] Few cases of central hyperthyroidism were excluded from the analyses. For each cardiovascular outcome associated with SHypo and SHyper, we updated our systematic review of the literature.[4,8–10] IPD analyses allow analysis of specific subgroups with potentially different risk profiles, while study-level meta-analyses may lead to aggregation biases with spurious subgroup data.[9] IPD analyses best pool evidence across studies; they allow (i) increase statistical power, (ii) adjust for similar confounding factors across studies, (iii) define similar TSH range, and (iv) standardize definitions of clinical outcomes.[45]

Current evidence for association between subclinical thyroid dysfunction and cardiovascular diseases

The Thyroid Studies Collaboration examined the association between subclinical thyroid dysfunction and CHD events/mortality and HF, and clarified conflicting data from earlier prospective cohorts.[46–48]

In a milestone IPD analysis of 11 prospective cohorts,[4] 6.2% of the 55 287 participants had SHypo, but the vast majority (n = 51 837) were euthyroid. A total of 4470 participants developed CHD events, among whom 430 (9.6%) had SHypo. Hazard ratios (HRs) for CHD mortality were: 1.09 (95% CI, 0.91–1.30) with TSH 4.5 to 6.9 mIU/L; 1.42 (95% CI, 1.03–1.95) for TSH 7.0–9.9 mIU/L; and 1.58 (95% CI, 1.10–2.27; P = 0.005 for trend) for TSH > 10 mIU/L (*Figure 4*). SHypo did not increase total mortality.

A similar IPD analysis on the association of SHypo and HF in 25 390 participants (8.1% with SHypo) found that HF risk increased both with higher and lower TSH (P for quadratic pattern < 0.01) (*Figure 4*); 2069 participants had HF events, of whom 250 (12.1%) had SHypo and 57 (2.8%) SHyper.[8]

An IPD analysis with 52 674 participants from 10 cohorts (4.2% with SHyper) showed an association between SHyper and total mortality (HR 1.24, 95% CI, 1.06–1.46), CHD mortality (HR 1.29, 95% CI, 1.02–1.62), CHD events (HR 1.21, 95% CI, 0.99–1.46), and AF (HR 1.68, 95% CI, 1.16–2.43). 3,653 participants had CHD events, of whom 108 (2.9%) had SHyper. In subgroup analyses of CHD mortality and AF, TSH < 0.10 mIU/L was associated with higher HR (2.54, 95% CI, 1.08–5.99).[10] Finally, an IPD analysis of 47,573 individuals from 17 cohorts (SHypo prevalence 0.4–16.3%, mean 7.3%) reported increased risk of fatal stroke in SHypo for those 18–49-years old (HR 4.22; 95% CI, 1.08–16.55) and 50–64-years old (HR 2.86; 95% CI, 1.31–6.26). A pattern of increased stroke risk for higher TSH levels was identified: In age- and sex-adjusted analyses the HR for fatal stroke was 1.18 (95% CI, 0.83–1.69) at TSH 4.5–6.9 mIU/L, 1.63 (95% CI, 1.09–2.43) at TSH 7.0–9.9 mIU/L, and 1.69 (95% CI, 0.88–3.27) at TSH 10.0–19.9 mIU/L.[9]

Impact of thyroid hormones replacement on cardiac function and cardiovascular imaging

Current data show several cardiac function parameters normalized in patients treated for SHypo.

Levothyroxine in SHypo decreased the ratio between pre-ejection period and LV ejection time decreased in 46 adults[50] and improved cardiac preload and contractility in 30 women.[51] In 10 patients with SHypo, IRT and the A wave dropped after treatment, and E/A ratio increased (1.3 ± 0.3 to 1.7 ± 0.4, $P < 0.001$)[36] (see Supplementary material online, *Table S1A*). Studies were limited by small sample size, short duration, non-standardized definitions of SHypo and echo measurements.

Impact of thyroid hormones replacement on CIMT

Some evidence (see Supplementary material online, *Table S1B*) shows CIMT regressed after thyroid function normalized. In a double-blind controlled trial, levothyroxine reduced CIMT from 0.76 ± 0.14 to 0.67 ± 0.13 mm ($P = 0.03$).[40] CIMT decreased from 0.67 ± 0.11 to 0.60 ± 0.10 mm ($P = 0.02$) in SHypo treated with levothyroxine for a year.[39] In a before–after trial including 34 patients with SHypo, CIMT decreased, after a year of levothyroxine replacement, from 0.64 ± 0.02 to 0.55 ± 0.02 mm ($P < 0.001$), total cholesterol from 5.99 ± 0.25 to 4.80 ± 0.20 mmol/L ($P < 0.001$); and low-density lipoprotein cholesterol (LDL-C) from 3.65 ± 0.23 to 2.75 ± 0.19 mmol/L ($P = 0.005$).[41]

Clinical issues for screening and treatment of subclinical thyroid dysfunction and the TRUST trial

Indications for screening and thresholds for treating SHypo and SHyper are uncertain because randomized clinical trials (RCTs) with relevant clinical outcomes are lacking[52–54] and information on long-term risks is limited.[55] Current evidence is mostly based on observational studies, but also guidelines, expert committees and small randomized trials which have systematically been reviewed by the US Preventive Services Task Force (USPSTF) in 2015.[56,57] Large randomized trials are needed to provide more evidence for screening and treatment of subclinical thyroid dysfunction.

The TRUST Trial, a blinded multicentre RCT funded by the EU-FP7 (Proposal 278148-2, *ClinicalTrials.gov*, NCT01660126), has been set up to investigate the multi-modal impact of treatment on quality of life and symptoms, and cardiovascular markers. Follow-up was continued until the end of 2016, shedding light on thresholds and benefits of levothyroxine in SHypo.

Recommendation for screening based on current evidence

Current guidelines[58,59] advocate measuring TSH for specific conditions.[4,8,49] Patients with previous thyroid disorder, hypothalamic-pituitary disorder, and history of autoimmune disease could benefit from TSH monitoring because they are at increased risk of overt hypothyroidism.[12] TSH testing could benefit those with abnormal values or changes in lipid profile,[60] hyponatremia, unclear elevation of creatinine kinase, anaemia, and thyroid altering medication since all these laboratory findings are associated with higher risk of thyroid dysfunction, especially hypothyroidism.[61] According to the USPSTF, there is currently insufficient evidence for weighing the benefits and harms of early screening.[56,57] The American Academy of Family Physicians and the American College of Physicians (ACP) recommend thyroid function be checked regularly in older women (>50 years for ACP). The American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) advocate assessing thyroid function in any patient at risk for hypothyroidism, and measuring TSH in those >60.[62]

Recommendation for treatment based on current evidence

Current recommended thresholds for starting thyroid hormone replacement are based on observational data and clinical trials with short follow-up. Their results suggest a TSH treatment threshold ≥ 10 mIU/L,[62] also recommended by the ATA and AACE. The decision to treat TSH < 10 mIU/l should be taken individually, according to the risk profile of each patient.[62] Patients with cardiovascular disorder or at high risk of developing overt hypothyroidism might benefit from earlier therapy,[1,62] though opinions conflict.[57] Some have argued for the use of liothyronine (synthetic triiodothyronine), either alone or in combination with levothyroxine, for better control of thyroid function; however, the current evidence is too short-term and limited to recommend this form of treatment.[63] Especially in older people, overtreatment is common and can cause severe adverse events like arrhythmia and HF exacerbation.[64] According to the ATA and AACE, treatment if TSH < 0.1 mIU/L might be reasonable in high-risk patients, including those with cardiac arrhythmias, or postmenopausal women at risk of or with known osteoporosis. In other cases, careful clinical and 6-monthly laboratory follow-up seems appropriate.[52]

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

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