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The Clinical Significance of Subclinical Thyroid Dysfunction

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Subclinical thyroid disease (SCTD) is defined as serum free T_4 and free T_3 levels within their respective reference ranges in the presence of abnormal serum TSH levels. SCTD is being diagnosed more frequently in clinical practice in young and middle-aged people as well as in the elderly. However, the clinical significance of subclinical thyroid dysfunction is much debated. Subclinical hyper- and hypothyroidism can have repercussions on the cardiovascular system and bone, as well as on other organs and systems. However, the treatment and management of SCTD and population screening are controversial despite the potential risk of progression to overt disease, and there is no consensus on the thyroid hormone and thyrotropin cutoff values at which treatment should be contemplated. Opinions differ regarding tissue effects, symptoms, signs, and cardiovascular risk. Here, we critically review the data on the prevalence and progression of SCTD, its tissue effects, and its prognostic implications. We also examine the mechanisms underlying tissue alterations in SCTD and the effects of replacement therapy on progression and tissue parameters. Lastly, we address the issue of the need to treat slight thyroid hormone deficiency or excess in relation to the patient's age. (*Endocrine Reviews* 29: 76–131, 2008)

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Abbreviations: AF, Atrial fibrillation; AFTN, autonomously functioning thyroid nodules; Apo, apolipoprotein; BMD, bone mineral density; BMI, body mass index; CHD, chronic heart disease; CHF, congestive heart failure; CI, confidence interval; CIMT, carotid artery IMT; CMR, cardiac MRI; CRP, C-reactive protein; D1, deiodinase type 1; DTC, differentiated thyroid cancer; E/A, early-to-late transmitral peak flow velocity ratio; ECG, electrocardiogram; FT3, free T_3; FT4, free T_4; HDL-C, high-density lipoprotein cholesterol; hsCRP, high sensitive CRP; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; LVET, left ventricular ejection time; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; OR, odds ratio; PEP, preejection period; SCTD, subclinical thyroid disease; SF-36, Health Short Form 36; SHyper, hyperthyroidism; SHypo, subclinical hypothyroidism; SRS, symptom rating score(s); SVR, systemic vascular resistance; TA, thyroid autoimmunity; TAFI, thrombin activatable fibrinolysis inhibitor; TC, total cholesterol; TgAb, antithyroglobulin antibody; TPO, thyroid peroxidase; TPOAb, antithyroid peroxidase antibody; VO_2, oxygen uptake; vWF, von Willebrand factor.

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I. Introduction

AS OUR ABILITY to detect ever more subtle degrees of thyroid dysfunction has improved with highly sensitive and specific assays, the concept of subclinical thyroid disease (SCTD) has emerged over the past several decades.

Although it is recognized that patients with SCTD may have subtle symptoms of thyroid dysfunction, the definition is purely a biochemical one: SCTD is defined as serum free T_4 (FT4) and total or free T_3 (FT3) levels within their respective reference ranges in the presence of abnormal serum TSH levels. Serum TSH is undetectable or low in subclinical hyperthyroidism (SHyper), and it is increased in subclinical hypothyroidism (SHypo) (1–4). As screening for thyroid disease becomes more common, SCTD is being diagnosed more frequently in clinical practice in young and middle-aged people as well as in the elderly. However, population screening and treatment of these conditions are controversial despite the high prevalence of SCTD and the potential progression to overt disease (5–7), because the risks of SCTD are uncertain and the benefits of treatment unproven. Opinions are quite divergent regarding the tissue effects, clinical symptoms and signs, and the cardiovascular risks of mild thyroid hormone excess or deficiency (5, 6, 8, 9).

At present, there is no consensus about the TSH concentration at which treatment should be contemplated (5, 6), except for elderly individuals with serum TSH values less than 0.1 mIU/liter (6). Moreover, because the definition of SCTD is based on abnormal TSH levels, the normal TSH range must be established, and it is proving to be a difficult task to define the upper limit of normal (10, 11). To compound the issue further, it has been difficult to correlate possible adverse effects at the tissue level with a TSH cut-off point, because of the individual set-point of the hypothalamic pituitary-thyroid axis (12).

Here we review clinical and epidemiological data to determine the: 1) prevalence and progression of SCTD; 2) global clinical risk (cardiovascular, bone, muscle, lipid, and hemostatic profile, *etc.*) associated with SCTD and its prognostic implications; 3) risks of untreated SCTD in relation to the patient's age; 4) benefits of correcting SCTD; 5) optimal treatment; and 6) benefits of a screening program. Lastly, an algorithm for the practical evaluation and treatment of SCTD examined from a global viewpoint is provided.

II. Methods

A. Identification of sources

We searched personal files, MEDLINE articles, and references of relevant articles and textbooks published from 1970 through April 2007 in the English language (including translated articles). For MEDLINE, we used the search terms: thyrotropin (TSH), L-thyroxine, replacement therapy, thyroid cancer, thyroid autonomy, TSH suppression, prevalence, progression, cardiovascular risk, heart, bone, osteoporosis, muscle, quality of life, symptoms, cognitive function, pregnancy, infertility, elderly, children, and the keywords hyperthyroidism, hypothyroidism, SCTD, subclinical hyperthyroidism (exogenous and endogenous), and subclinical hypothyroidism.

B. Methods of evaluation to assess study quality

The two authors agreed on the inclusion/exclusion status of the studies reviewed after assessing the quality of studies. Although this review is not a meta-analysis, we critically assessed the literature and tried to identify high-quality studies. The TSH range at baseline evaluation was recorded to determine the degree of thyroid hormone deficiency or excess that was considered in each study. In the evaluation of treatment for SCTD, wherever possible, preference was given to randomized controlled trials and longitudinal studies; however, very few reports had these characteristics. Therefore, we included other types of clinical trials. Moreover, we examined whether the control group was appropriate, whether euthyroidism was completely obtained after treatment of SCTD, and whether over- or undertreatment was avoided. Furthermore, we evaluated whether the methods used to evaluate the effects of SCTD at tissue level were correct. Lastly, we evaluated whether a correct statistical analysis was applied in the studies. Previously published review articles evaluating the effects of SCTD are discussed.

III. Normal Thyrotropin-Stimulating Hormone Range

Because SCTD is only detected as a TSH abnormality, the definition of the TSH reference range is critical (13, 14). Over the last three decades, the upper reference limit for TSH has declined from about 10 mIU/liter with the first-generation TSH RIAs to about 4.0–4.5 mIU/liter with subsequent TSH assays and the use of thyroid antibody tests to prescreen subjects. The normal TSH range has long been debated (10, 11, 13–15). This issue also impacts on the TSH target level for replacement thyroid hormone therapy in patients with hypothyroidism, the treatment of patients with mild thyroid hormone deficiency, and screening to detect SCTD.

TSH in the circulation is heterogeneous with respect to both glycosylation and biological activity. Assays vary widely because current TSH immunometric assays involve the use of monoclonal antibodies that differ in specificity and may measure different TSH isoforms. Thus, the variation in the reference intervals obtained with different methods reflects differences in epitope recognition of different TSH isoforms. These differences make it difficult to establish a universal upper TSH reference limit. Lymphocytic infiltration of the thyroid gland is present in up to 40% of healthy women. Moreover, the National Health and Nutritional Examination Survey (NHANES) III survey, which used a competitive immunoassay procedure, reported an antithyroglobulin antibody (TgAb) prevalence of 10% and detectable thyroid peroxidase (TPO) levels in 12% of the general population (16). Furthermore, a hypoechoic ultrasound pattern or an irregular echo pattern may precede antithyroid peroxidase antibody (TPOAb) positivity in autoimmune thyroid disease, and TPO may not be detected in more than 20% of individuals with ultrasound evidence of thyroid autoimmunity (TA) (17, 18). For this reason, it is recommended that the serum TSH reference interval be established using blood sampled in the morning from fasting euthyroid subjects who have no family history of thyroid disease, are not taking medication, have no visible or palpable goiter or pathological thyroid ultrasonography findings, and are not positive for TPOAb or TgAb (19). For example, in the NHANES III study, in subjects without reported thyroid disease, TPOAb fre-

quency increased as TSH levels increased in the study population (being 5.5% at TSH 0.4–1.0 mIU/liter, 30.6% at TSH 3.5–4.0 mIU/liter, and 80–90% in subjects with a TSH concentration over 10 mIU/liter (20). Further evidence of a relationship between TPOAb and serum TSH comes from a Norwegian study (21). In this health survey, all inhabitants 20 yr and older (n = 94,009) in Nord-Trøndelag were evaluated by a questionnaire and blood samples. In individuals without a history of thyroid disease, the median and the 2.5th and 97.5th percentiles for TSH were 1.80 and 0.49–5.70 mIU/liter for females and 1.50 and 0.56–4.60 mIU/liter for males. However, when individuals with positive TPOAb were excluded, the 97.5th percentiles dropped to 3.60 and 3.40 mIU/liter for females and males, respectively. Moreover, the percent of TPO-positive subjects was lowest in the TSH range between 0.2 and 1.9 mIU/liter and increased with both lower and higher levels of TSH (21).

In the NHANES III study, a separate population of 13,344 subjects without a history of thyroid disease, goiter, pregnancy, or biochemical hypo- or hyperthyroidism; not taking thyroid medication, androgens, or estrogens; and free of anti-TPO and TgAb (the so-called "reference population") was examined separately from the entire cohort of 17,353 persons. In this group without thyroid disease or risk factors, the median TSH level was 1.39 mIU/liter and the 2.5th and 97.5th percentiles were 0.45 and 4.12 mIU/liter, respectively (16). However, TSH values did not have a Gaussian distribution, and about 9% of the subjects in this reference population had TSH levels above 2.5 mIU/liter. Although it may be conjectured that this "upper tail" was observed because the group included people with occult TA and negative anti-TPO antibodies, other recent data argue against this explanation.

Evidence against occult autoimmunity being responsible for the "tail" in the TSH distribution comes from a recent German study that established reference intervals for TSH based on National Academy of Clinical Biochemistry criteria as well as sonographic confirmation of a normal thyroid gland (19). Of the 870 apparently healthy persons investigated, only 453 were included in the study; 47.9% of healthy blood donors did not meet all criteria for normal thyroid function and morphology by sonography. In this reference group, the lower limit of reference range for TSH increased from 0.3 to 0.4 mIU/liter, and the upper reference limit decreased from 4.1 to 3.7 mIU/liter compared with the NHANES III study. However, serum TSH levels were not Gaussian in this study either, which suggests that the upper tail may be a biological phenomenon, possibly related to TSH receptor gene polymorphisms or TSH microheterogeneity. Of course, occult thyroid disease that cannot be detected by antibody testing and thyroid sonography can never be completely ruled out. Moreover, iodine intake may affect the reference interval for thyroid function tests. The differences between the German and U.S. data could be related to the higher incidence of Hashimoto disease in the United States or because of higher iodine intake or increased thyroidal autonomy in the possibly mildly iodine-deficient German population. Despite iodine supplementation programs, iodine deficiency persists in some European countries. In a cross-sectional epidemiological survey in a previously iodine-deficient area (western Pomerania, northeast Germany), the reference interval for serum TSH was 0.25–2.12 mIU/liter, and the reference intervals for serum TSH and free thyroid hormones were narrower and moved to the left when compared with the NHANES study (22). In an iodine-deficient village of southern Italy, the entire resident population underwent thyroid function tests, thyroid ultrasound examination, and measurement of urinary iodine concentration (23). The mean serum TSH concentration in the adult population was 1.4 ± 1.1 mIU/liter in goitrous subjects and 2.0 ± 2.4 mIU/liter in nongoitrous subjects (23).

Evidence in support of a narrower normal TSH range comes from the Whickham survey (24). This 20-yr follow-up study of hypothyroidism in 1700 subjects demonstrated a higher prevalence of progression to overt disease in patients with TSH levels above 2 mIU/liter. However, the risk was far higher in those subjects who had positive antithyroid antibodies at baseline.

Conflicting results have been reported about the association between TSH at the upper limit of the considered normal range and cardiovascular risk factors (25–38). Subjects with high-normal serum TSH (2.0–4.0 mIU/liter) and positive thyroid autoantibodies had higher mean serum cholesterol levels than those with TSH values in the lower half of the normal range (0.40–1.99 mIU/liter) (25). Moreover, administration of T_4 to the subjects with high-normal serum TSH was accompanied by a significant lowering of cholesterol and low-density lipoprotein cholesterol (LDL-C), but only in antibody-positive subjects (25). In the fifth Tromso study (a cross-sectional epidemiological study of 5143 subjects), there was a significant, positive correlation between serum TSH levels and serum total cholesterol (TC) and LDL-C levels in men and women (26). However, this did not reach statistical significance in women after adjusting for age and body mass index (BMI). In an interventional study, which included subjects with SHypo receiving T_4 supplementation for 1 yr (32 subjects given placebo and 32 subjects given T_4), serum TC and LDL-C levels were significantly reduced after T_4 therapy in subjects with SHypo, including those who at the end of the study had serum TSH levels between 0.2 and 2.0 mIU/liter (26).

The association between TSH within the reference range and serum lipid concentration was evaluated in a large cross-sectional population-based study of 30,656 individuals without known thyroid disease (27). Total serum cholesterol, LDL-C, non-high-density lipoprotein cholesterol (HDL-C), and triglycerides increased consistently with increasing TSH (P for trend < 0.001), whereas HDL-C decreased consistently (P for trend < 0.001). The association with serum lipids was linear across the entire reference range, with no indication of any threshold effect. Moreover, the associations with triglycerides and HDL-C were stronger among overweight than among normal-weight individuals (27).

Studies evaluating whether thyroid function within the euthyroid TSH range can affect blood pressure have produced conflicting results (28–33). The relation between thyroid function and blood pressure was assessed in 284 subjects (68% hypertensive) who consumed high- and low-sodium diets. The serum FT4 index was lower ($P < 0.0001$) and the TSH concentration higher ($P = 0.046$) in hypertensive than in normotensive subjects, irrespective of other baseline char-

acteristics, and the FT4 index independently predicted salt sensitivity of blood pressure (28). Similarly, a population-based study showed that small differences in serum TSH (within and above the reference range) were associated with significant differences in diastolic blood pressure (29). The relation between serum TSH and blood pressure was also assessed in the recent Tromso study, a population-based health survey, which included 5872 subjects not using blood pressure or T_4 medication (30). In this study, there was a modest but significant positive correlation between serum TSH within the normal range (0.2–4.0 mIU/liter) and both systolic and diastolic blood pressure (30).

However, in a cross-sectional study of 2033 individuals in the Busselton thyroid study, mean systolic blood pressure, diastolic blood pressure and the prevalence of hypertension did not differ between subjects with SHypo and euthyroid subjects, nor did they differ between subjects with serum TSH concentrations in the upper reference range (2.0–4.0 mIU/liter) and those with TSH concentration in the lower reference range (0.4–2.0 mIU/liter) (31). On the other hand, a linear and positive association between TSH and systolic and diastolic blood pressure was found in a recent cross-sectional, population-based study on 30,728 individuals without previously known thyroid disease (32). Comparing TSH of 3.0–3.5 mIU/liter (upper part of the reference) with TSH of 0.50–0.99 mIU/liter (lower part of the reference), the odds ratio (OR) for hypertension was 1.98 [95% confidence interval (CI), 1.56 to 2.53] in men, and 1.23 (95% CI, 1.04 to 1.46) in women (32). In addition, a measure of endothelial function, flow-mediated endothelium-dependent vasodilatation of the brachial artery, was lower in healthy individuals with a serum TSH concentration between 2.0 and 4.0 mIU/liter than in those with TSH values between 0.4 and 2.0 mIU/liter (33).

Conflicting results have also been reported about the association between thyroid function and the BMI in individuals with TSH and FT4 within normal range (34–37). A cross-sectional population study examined the association between the category of serum TSH or serum thyroid hormones and BMI or obesity (34). There was a positive association between obesity (BMI > 30 kg/m^2) and serum TSH levels ($P = 0.001$). Moreover, there was a negative association between BMI and serum FT4 ($P < 0.001$) and no association between BMI and serum FT3 levels. The difference in BMI between the groups with the highest and lowest serum TSH levels was 1.9 kg/m^2, which corresponds to a difference in body weight of 5.5 kg among women. The results of this study suggest that even slightly elevated serum TSH levels are important in determining body weight in the population (34). Among 87 obese women (BMI > 30 kg/m^2), serum TSH concentrations were positively associated with increasing BMI, but there was no relationship between serum FT4 and BMI (35). Furthermore, in 6164 subjects living in Tromso, TSH concentrations were positively associated with BMI in women and men who did not smoke (36). However, in 401 euthyroid subjects there was no association between thyroid status within the normal range and BMI and no difference in BMI when subjects were stratified according to serum TSH or FT4 (37). Lastly, there was no difference in serum TSH or FT4 between lean and obese euthyroid subjects (37).

There are no prospective long-term studies to suggest increased risks of cardiovascular morbidity or mortality in patients with TSH levels at the upper limit of the considered normal range. A recent community-based study carried out in Busselton, Western Australia, examined whether serum TSH in the upper reference range (2.0–4.0 mIU/liter) was associated with cardiovascular end-points (38). The prevalence of coronary heart disease was not higher in subjects with a serum TSH level in the upper normal range (>2.0 mIU/liter) than in euthyroid controls (0.4–2.0 mIU/liter). Similarly, it did not differ between subjects with and those without thyroid antibodies (38).

In summary, the strongest epidemiological evidence for lowering the TSH normal range is the higher rate of antithyroid autoimmunity in subjects with TSH between 3 and 4.5 mIU/liter and the higher rate of progression to overt thyroid disease in this subgroup. Arguments in favor of lowering the upper limit of the TSH normal range are the cost of monitoring patients with thyroid autoantibodies and a TSH concentration between 3.0 and 4.5 mIU/liter, the risk of progression to overt disease, and the potential morbidity in subjects lost to follow-up.

Arguments against lowering the upper limit of normal include the fact that mild elevations in serum TSH are sometimes reversible (39), the expense of therapy without proven benefit, and the possibility of overtreatment leading to iatrogenic hyperthyroidism. In fact, links between TSH at the upper limit of normal range and some important cardiovascular risk factors are either conflicting or inconclusive (25–38). Moreover, the evidence in support of lowering the upper limit of the TSH normal range should be weighed against the health and economic impact that a reduced TSH range would have (11). About 10% of the 25,862 individuals screened in the Colorado study had mild thyroid failure, namely a TSH level above the laboratory upper limit of 5.1 mIU/liter (40). About 74% of those subjects had TSH levels between 5.0 and 10.0 mIU/liter. Given these figures, about 13 million people in the United States may have undiagnosed SHypo. A decrease in the upper limit of the TSH reference range from 5 to 3 mIU/liter would result in an increase of more than 3.0- to 5.0-fold in the percentage of patients classified as having mild thyroid disease (41).

A more convincing demonstration of the positive impact on patient outcome in identifying and treating persons with TSH levels in the upper normal range is necessary before lowering the upper limit of normal for serum TSH. In addition, it must be recognized that a normal range upper or lower limit, based on a reference population, does not of necessity mean that any person who falls outside that limit requires treatment or has an illness. In the meantime, careful follow-up should be considered for asymptomatic patients with serum TSH levels between 3 and 4.5 mIU/liter, especially if they have positive anti-TPO antibodies.

IV. Set-Point of the Hypothalamic-Pituitary-Thyroid Axis and Individual TSH Range

The finding that individuals have a set-point of the hypothalamic-pituitary-thyroid axis was a breakthrough in our

understanding of SCTD (12). The relationship between serum FT4 and TSH in an individual can be considered to establish the individual's hypothalamic-pituitary-thyroid axis "set-point." Andersen *et al*. (12) measured serum TSH concentrations each month in 16 healthy male volunteers and found that the width of individual 95% CI of TSH values was approximately half that of the whole group. Consequently, it is theoretically possible that a test result may be abnormal for an individual but still be within the laboratory reference limit.

Interindividual differences in the hypothalamic-pituitary-thyroid axis set-point are genetically determined (42, 43). Moreover, genetic variants have been found to affect both blood pressure and serum TSH levels (44). Consequently, interindividual differences in the hypothalamic pituitary-thyroid axis set-point might explain the different symptoms, signs, and peripheral thyroid hormone effects in subjects with exactly the same hormonal pattern. Furthermore, the biological activity of thyroid hormone, in terms of T_3 availability, is regulated by type 1, 2, and 3 iodothyronine deiodinases (D1, D2, and D3) (45). The efficiency of conversion of T_4 to T_3 by D2 increases as the serum T_4 decreases (45). Consequently, in the presence of a low level of T_4 or in case of a hypothyroid state, D2 is increased and can generate a significant quantity of plasma T_3. Moreover, polymorphisms in genes involved in thyroid hormone metabolism may affect thyroid hormone bioactivity (46). Deiodinases are tissue specifically regulated, and this may have consequences for the peripheral effects of thyroid hormone and for set points of endocrine feedback regulation (47).

In conclusion, a serum TSH level within the normal range, even if it is below 2.5 mIU/liter, may not be as sensitive a parameter of thyroid dysfunction for individual subjects as had previously been thought. Therefore, it is important to evaluate and integrate the laboratory results in relation to the clinical assessment, *e.g*., the patient's symptoms, physiological status (*e.g*., age, pregnancy, *etc*.), and underlying health status (other comorbidities and drug intake).

V. Subclinical Hypothyroidism

A. Subclinical hypothyroidism and minimally increased TSH

SHypo represents a condition of mild to moderate thyroid failure characterized by normal serum levels of thyroid hormones with mildly elevated serum TSH concentrations (1–2). A panel of experts recently divided patients with SHypo into two categories: patients with mildly increased serum TSH levels (4.5–10 mIU/liter), and patients with more severely increased serum TSH levels (>10 mIU/liter) (6). We shall examine the progression of the disease, the adverse effects, and treatment using these definitions of thyroid hormone deficiency.

B. Etiology of subclinical hypothyroidism

The etiology of SHypo is the same as the etiology of overt hypothyroidism (1, 2)(Table 1). It is most often caused by chronic lymphocytic thyroiditis (goitrous Hashimoto's thyroiditis and atrophic thyroiditis), an autoimmune disorder of the thyroid gland that is the most common cause of decreased thyroid hormone production in patients with acquired mild, subclinical, or overt hypothyroidism (2, 48–50). Other causes of primary hypothyroidism may result from therapies that destroy thyroid tissue such as radioactive iodine treatment or external radiation therapy. Mild and overt hypothyroidism are common after external radiotherapy of the head and neck area and develops gradually within the first year with a risk that appears to be dose-dependent (51). It is frequent after external radiation therapy in patients with Hodgkin's lymphoma, leukemia, aplastic anemia, brain tumors, or bone marrow transplantation. Chemotherapy also may induce hypothyroidism in patients with lymphoma (52). Women with breast cancer may have an increased risk of autoimmune thyroid disease after adjuvant chemotherapy and tamoxifen (53, 54). Transient or persistent increases in serum TSH may occur after subacute, postpartum, or painless thyroiditis and after partial thyroidectomy.

TABLE 1. Causes of subclinical hypothyroidism

Chronic autoimmune thyroiditis (risk factors: family history of autoimmune thyroid disease, personal or family history of associated autoimmune disorders, Down syndrome, Turner's syndrome)
Persistent TSH increase in subacute thyroiditis, postpartum thyroiditis, painless thyroiditis
Thyroid injury: partial thyroidectomy or other neck surgery, radioactive iodine therapy, external radiotherapy of the head and neck
Drugs impairing thyroid function: iodine and iodine-containing medications (amiodarone, radiographic contrast agents), lithium carbonate, cytokines (especially interferon α), aminoglutetimide, ethionamide, sulfonamides, and sulfonylureas
Inadequate replacement therapy for overt hypothyroidism [inadequate dosage, noncompliance, drug interactions (iron, calcium carbonate, cholestyramine, dietary soy, fiber, *etc*.), increased T_4 clearance (phenytoin, carbamazepine, phenobarbital, *etc*.), malabsorption]
Thyroid infiltration (amyloidosis, sarcoidosis, hemochromatosis, Riedel's thyroiditis, cystinosis, AIDS, primary thyroid lymphoma)
Central hypothyroidism with impaired TSH bioactivity
Toxic substances, industrial and environmental agents
TSH receptor gene mutations; Gα gene mutations

Several drugs may induce subclinical or overt hypothyroidism particularly in patients with underlying autoimmune thyroiditis (iodine-containing compounds, lithium carbonate, cytokines, and interferon) (2, 51). Amiodarone, a benzofuranic-derivative, iodine-rich drug used to treat tachyarrhythmias, can inhibit thyroid hormone production. The chronically high iodine intake induced by amiodarone administration may increase the prevalence of chronic autoimmune thyroiditis in genetically susceptible individuals or may precipitate hypothyroidism in patients with autoimmune thyroiditis. Iodine-induced subclinical or overt hypothyroidism may develop in patients treated with amiodarone, particularly in areas of high iodine intake (55). Excess dietary iodine, medication, topical antiseptics, and iodine-contrast agents used for diagnostic procedures may induce mild or transient hypothyroidism. Lithium carbonate, which is prescribed for the treatment of manic-depressive disorders, may impair thyroid hormone synthesis and release and

may be associated with the development of goiter (40–60% of cases) and mild or moderate hypothyroidism (56–58). Patients who develop persistent hypothyroidism during lithium treatment are more likely to have underlying chronic Hashimoto thyroiditis.

Interferon-α, used for the treatment of hepatitis or certain tumors, alone or in combination with IL-2, may induce thyroid dysfunction due to the activation or enhancement of the autoimmune process (51, 59). Risk factors associated with the possible development of hypothyroidism include female sex, longer duration of interferon-α treatment, presence of chronic hepatitis C virus, older age, and preexisting presence of anti-TPO antibodies. The prevalence of interferon-α-associated hypothyroidism in patients with chronic hepatitis C virus is reported to be between 7 and 39%, and the presence TPO antibodies may be an important risk factor (51) that predicts persistent hypothyroidism at the end of interferon-α treatment. TA and dysfunction frequently occur in multiple sclerosis patients during interferon-β therapy, particularly within the first year of treatment; thyroid dysfunction is generally subclinical and transient in over half of the cases (60).

Hypothyroidism may develop during treatment with aminoglutethimide, ethionamide, sulfonamides, and sulfonylureas, which interfere with thyroid hormone synthesis (51). Persistent primary hypothyroidism and transient, mild TSH elevation are frequent complications of sunitinib therapy, an oral tyrosine kinase inhibitor recently approved for the treatment of gastrointestinal stromal tumors and renal cell carcinoma (61). Toxic injury to the thyroid gland was reported after exposure to various pesticides, herbicides, industrial chemicals, and naturally occurring environmental chemicals (51). Infiltrative disease (Riedel's thyroiditis, amyloidosis, hemochromatosis, and cystinosis) or infectious disorders of the thyroid gland (*Pneumocystis carini* infection and Kaposi's sarcoma in patients with AIDS) may induce thyroid hormone deficiency; however these diseases rarely cause hypothyroidism (51).

The postpartum period is associated with an increased risk of developing subclinical or overt hypothyroidism. Similarly, subjects with a family history of autoimmune thyroid disorders, autoimmune endocrine diseases, and nonendocrine autoimmune disorders (vitiligo, pernicious anemia, celiac disease, atrophic gastritis, multiple sclerosis, *etc.*) have an increased risk of hypothyroidism (62–64). Autoimmune thyroiditis can be associated with other endocrine deficiency syndromes: polyendocrine failure syndrome type 1, which includes hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis; and polyendocrine failure type 2, which includes adrenal insufficiency, type 1 diabetes mellitus, and primary ovarian failure.

SHypo is frequently observed in patients with overt hypothyroidism receiving inadequate replacement therapy due to poor compliance, drug interactions, or inadequate monitoring of therapy. In fact, between 17.6 and 30% of patients with overt thyroid failure were reported to have SHypo due to inadequate thyroid hormone supplementation (40, 65).

Germline loss-of-function mutations in one or both alleles of the TSH-receptor gene can cause SHypo (66, 67). TSH was slightly (6.6–14.9 mIU/liter) to moderately (24–46 mIU/liter) increased in these patients and was associated with normal free thyroid hormone concentrations, normal thyroid size, and normal biochemical parameters of TA (67). Recently, a low prevalence of TSH receptor mutations was reported in a large series of subjects with sporadic and familial nonautoimmune SHypo (68). However, TSH receptor mutations should be considered in subjects with a familial TSH increase associated with normal thyroid ultrasound and without markers of TA.

C. Differential diagnosis of serum TSH elevation

Only persistent or progressive SHypo should be considered an early stage of thyroid disease. It may be difficult to distinguish between transient disturbances of thyroid gland function and mild thyroid failure (Table 2). Transient hypothyroidism, followed by a euthyroid state, may be due to thyroiditis caused by viral infection (subacute thyroiditis) or autoimmunity (postpartum, painless, or silent thyroiditis). In the early phase of the disease, a mild TSH increase with absent or mild symptoms of hypothyroidism may make it difficult to distinguish who will recover from those destined to be permanently hypothyroid. Moreover, evidence from a long-term follow-up of patients with subacute thyroiditis suggests that viral infection can precipitate an autoimmune thyroid disease in susceptible individuals, thereby resulting in the development of permanent hypothyroidism (51). A diagnosis of persistent SHypo can be verified by reevaluating TSH concentration after 6 or 12 months. This will ensure that only persistent or progressive disease is treated, and will also rule out the possibility that abnormal values were due to a laboratory error. A high thyroid autoantibody titer associated with an increased persistent serum TSH concentration may be useful to identify individuals with autoimmune thyroid disease who are at increased risk of developing permanent hypothyroidism.

It is important to identify transient TSH elevations caused by drugs that interfere with the central neurodopaminergic pathway, such as metoclopramide and phenothiazines (69, 70). A transient increase in TSH is common in hospitalized patients during the recovery phase of euthyroid sick syndrome (71). TSH concentrations may be falsely increased in some assays because of the presence of heterophilic antibodies against mouse proteins (72). Patients with untreated adrenal insufficiency may have high serum TSH concentrations (73). Rare causes of slightly high TSH concentrations are TSH-secreting pituitary adenomas or isolated pituitary resistance to thyroid hormone (74), however in this case the

TABLE 2. Serum TSH increase not associated with persistent SHypo

Transient SHypo following subacute, painless, or postpartum thyroiditis
After withdrawal of thyroid hormone therapy in euthyroid patients
Laboratory analytical problem (assay variability, heterophilic antibodies)
Impaired renal function
Recovery phase of euthyroid sick syndrome
Untreated adrenal insufficiency
TSH-secreting pituitary adenoma
Isolated pituitary resistance to thyroid hormone

increased TSH is associated with elevated serum T_4 and T_3 levels.

Central hypothyroidism can present with mild TSH elevation (5–10 mIU/liter) in approximately 25% of cases that may represent bioinactive TSH (2). The association of low serum thyroid hormone levels with normal or slightly high serum TSH has often been observed in patients with pituitary or hypothalamic disorders.

D. Prevalence of subclinical hypothyroidism

The prevalence of SHypo has been reported to be between 4 and 10% of adult population samples (16, 40, 65, 75–79). Two large population-based screening studies have provided important epidemiological data about SHypo: the Whickham Survey (75), and NHANES III (16). A third important large study, the Colorado Thyroid Prevalence Study (40), was not truly population-based. In the Whickham Survey (2779 subjects), SHypo, defined by serum TSH levels above 6 mIU/liter, was identified in 7.5% of females and 2.8% of males (75). TSH levels did not vary with age in males but increased markedly in females after the age of 45 yr. Serum TSH concentration was not age-related in women without antithyroid antibodies.

The sample examined in NHANES III (16,353 people aged $\geq$ 12 yr) represented the geographic and ethnic distribution of the U.S. population (16). SHypo was found in 4.3% of this population (normal TSH range, 0.39–4.6 mIU/liter). TPOAb were significantly associated with thyroid failure, were more prevalent in women than in men, increased with age, and were more prevalent in whites than in blacks.

In the Colorado study (over 25,000 state residents attending a series of statewide health fairs), 9.5% of all subjects had an elevated serum TSH concentration (normal range, 0.3–5.1 mIU/liter), and 89% of these were not on thyroid hormone therapy (40). Seventy-five percent of these individuals had serum TSH levels in the 5–10 mIU/liter range. In each age decade, a higher percentage of women than men had an elevated serum TSH concentration; the difference was significant after age 34 yr ($P > 0.01$). In the ninth decade of life, the prevalence of elevated TSH was as high as 15–20%.

The prevalence of mild thyroid dysfunction was higher in older populations in all epidemiological surveys conducted so far (16, 40, 65, 75–80). Elevated values of serum TSH (>6 mIU/liter) were found in 6.73% of subjects in a healthy urban population over the age of 55 yr in which a highly sensitive serum TSH assay was used to screen 968 subjects (79). Using a very sensitive assay, Parle *et al.* (76) measured serum TSH concentrations in 1210 patients aged over 60 yr registered with a single general practice. High TSH values occurred more frequently in females (11.6%) than in males (2.9%), and antithyroid antibodies were identified in 60% of patients with high TSH concentrations (76). In a study of 370 patients (287 women, 83 men) between 60 and 97 yr of age, after excluding patients with a history of thyroid disease, 14.6% of the women and 15.4% of the men had SHypo (78).

SHypo is more frequent in areas of iodine sufficiency, *i.e.*, 4.2% in iodine-deficient areas compared with 23.9% in areas of abundant iodine intake (80). This finding was confirmed by a high prevalence of SHypo in Iceland (18%) and Hungary (24%), which have a high iodine intake (81). Similarly, the incidence rate of overt hypothyroidism was lower than that of hyperthyroidism in an area with moderately low iodine intake (82). Iodine supplementation of a population may increase the incidence of thyroid hormone deficiency (83, 84).

In conclusion, SHypo represents a common disorder. The wide range (4–10%) of its prevalence might be due to the TSH cutoff used to define SHypo and differences in age, gender, and dietary iodine intake in the populations studied.

E. Natural history of subclinical hypothyroidism

In the 20-yr follow-up of the Whickham cohort, an increased serum TSH level was predictive of progression to overt hypothyroidism (24). Old age, female sex, and TPO antibodies were also associated with an increased risk of progression to overt hypothyroidism. The annual rate of progression to overt hypothyroidism was 4.3% in women with both raised serum TSH and antithyroid antibodies, 3% if only serum TSH was raised, and 2% if only antithyroid antibodies were present. A serum TSH level above 2 mIU/liter was associated with an increased probability of overt hypothyroidism (24). Thyroid autoantibodies were found to have prognostic relevance in other studies carried out in elderly subjects (76, 85–90). Rosenthal *et al.* (89) reported that one third of geriatric patients developed overt hypothyroidism during 4 yr of follow-up. Among these, overt hypothyroidism developed in all subjects with initial TSH levels above 20 mIU/liter, and 80% of those with high-titer thyroid antimicrosomal antibodies (regardless of initial TSH level) became overtly hypothyroid (89).

Several possible prognostic factors for overt hypothyroidism were analyzed in a prospective study of 82 women with increased TSH concentrations due to autoimmune thyroiditis, radioiodine treatment, or thyroidectomy, over a mean observation period of 9.2 yr with annual follow-up (90). After 10 yr, 28% of the women had developed overt hypothyroidism, and 68% remained in the subclinical stage. TSH value became normal in 4% (all from the group with TSH between 4–6 mIU/liter). According to the initial serum TSH concentrations (TSH 4–6, >6–12, and >12 mIU/liter), Kaplan-Meier estimates of the incidence of overt hypothyroidism were 0, 42.8, and 76.9%, respectively, after 10 yr ($P > 0.0001$). In the entire population, the risk of hypothyroidism was higher in patients with TSH levels above 6 mIU/liter and positive antimicrosomal antibodies (90).

In another prospective study, serum TSH was the most powerful predictor of the outcome of spontaneous SHypo in 107 subjects over the age of 55 yr with SHypo and no history of thyroid disease (91). Twenty-eight patients (26.8%) developed overt hypothyroidism, and 40 (37.4%) normalized their TSH values. The incidence rate of overt hypothyroidism was 9.91 cases per 100 patient-years in the whole population, and 1.76, 19.67, and 73.47 cases per 100 patient-years in subjects with initial TSH values between 5.0–9.9, 10.0–14.9, and 15.0–19.9 mIU/liter, respectively. A stepwise multivariate Cox regression analysis showed

that the only significant factor for progression to overt hypothyroidism was serum TSH concentration ($P < 0.0001$). The same authors analyzed the time course of normalization of TSH levels in 40 patients (32 women, mean age 62.8 ± 8.2 yr) with spontaneous SHypo (TSH > 5 mIU/liter and normal FT4) during a mean (±SD) observation period of 38.3 ± 17.0 months (range, 12–72 months) (39). The rate of normalization was greater in patients who had lesser degrees of serum TSH elevations and negative antithyroid antibody titers. Thus, the rate of normalization was 52% for those with serum TSH values between 5.0 and 9.9 mIU/liter and only 13% for those with TSH values between 10 and 14.9 mIU/liter. Fifteen patients (37.5%) normalized their TSH levels during the first year of follow-up and 27 (67.5%) during the first 2 yr. Ten patients (25%) had decreased TSH values at the fourth or fifth years of follow-up. However, the final spontaneous TSH normalization was in the range of 3 to 5 mIU/liter. Most subjects (65%) ended with TSH values higher than 3 mIU/liter, and 12 patients (30%) had values above 4.12 mIU/liter; only a minority of patients (10%) showed a reversion to TSH less than 2 mIU/liter (39). Finally, in another study, 11 of 21 octogenarians with SHypo and a TSH value greater than 4.7 mIU/liter had normal thyroid function after 3 yr (92).

A high risk of disease progression was observed in pregnant women with asymptomatic autoimmune thyroiditis (93). Women with autoimmune thyroiditis had basal TSH values significantly higher, albeit still normal, in the first trimester (1.6 *vs.* 0.9 mIU/liter; $P < 0.001$) than did women with healthy pregnancies used as controls. Despite a 60% average reduction in TPOAb titers during gestation, serum TSH remained higher in women with autoimmune thyroiditis than in controls throughout gestation: at delivery, 40% of cases had serum TSH levels above 3 mIU/liter, and 16% had serum TSH levels above 4 mIU/liter. A TRH test carried out in the days after parturition showed an exaggerated response in 50% of the cases.

The risk of progression from subclinical to overt hypothyroidism is less common in children and adolescents, and the recovery of thyroid function is more frequent. In 18 children and adolescents with autoimmune thyroiditis and elevated TSH, seven patients were euthyroid, 10 continued to have SHypo, and one became hypothyroid after a follow-up period of 5.8 yr (94). In another study, about 25% of adolescents affected by goitrous thyroiditis had spontaneous resolution of the disease over 20 yr, and about 33% developed overt hypothyroidism (95).

In conclusion, progression from mild to overt hypothyroidism may be related to the cause of thyroid hormone deficiency, the basal TSH value, and the patient's age. Moreover, SHypo may be a persistent or transient disease (96). Transient expression of TSH-receptor blocking antibodies may explain the recovery of thyroid function in some cases (2). On this basis, it may be reasonable to reevaluate patients with previously diagnosed SHypo to assess whether it is persistent. This may be accomplished by progressive reduction in L-T_4 dosage followed by serial TSH testing.

F. Symptoms, quality of life, and cognitive function in subclinical hypothyroidism

The decision to treat patients with SHypo is often based on the assessment of the clinical symptoms and signs of mild disease. A number of validated instruments are available to evaluate the presence or absence of various symptoms and signs of thyroid hormone deficiency (which are less sensitive in mild disease than in overt disease) or to evaluate mood, cognition, or quality of life. Moreover, the clinical picture of hypothyroidism has changed in recent years because of an earlier diagnosis. Formerly, the classical clinical picture of hypothyroidism focused on severe, long-standing disease. Thus, old clinical scoring systems may not identify symptoms and signs of very early disease, even if present. To complicate the issue further, nonspecific symptoms that occur in hypothyroidism are present commonly in persons with normal thyroid function or TA (97–99). Another obscure issue is the possible link between depression and impaired thyroid function (100, 101). This association is further complicated by evidence that autoimmune thyroiditis is more frequent in depressed patients than in healthy euthyroid individuals (20 *vs.* 5%) (102)

The groups of Billewicz (103) and Seshadri (104) have developed symptom scores to investigate the value of symptoms in discriminating overt hypothyroidism from euthyroidism, and these systems have also been applied to investigate the potential clinical significance of SHypo. In the Colorado study, a questionnaire that included 17 thyroid symptoms revealed a clear correlation between the type of symptom (dry skin, poor memory, slow thinking, muscle weakness, fatigue, muscle cramp, cold intolerance, puffy eyes, constipation, and hoarseness), the number of symptoms, and elevated TSH (40, 105). A small increase in total symptoms was observed with progressive deterioration of thyroid function. In fact, whereas euthyroid subjects reported a mean of 12.1% of all listed symptoms, overtly hypothyroid subjects had 16.6% of these symptoms ($P < 0.05$ *vs.* euthyroid group), and subjects with mild hypothyroidism had 13.8% ($P < 0.05$ *vs.* euthyroid group). Moreover, reporting more symptoms, in particular recently "changed symptoms" increased the likelihood of disease.

Using a new clinical score constituted by 14 symptoms and signs of hypothyroidism to assess the severity of thyroid failure, Zulewski *et al*. (106) found a good correlation between this score, FT4, and TSH in patients with SHypo. However, thyroid status was not predicted from clinical signs and symptoms in a retrospective study conducted in a primary care geriatrics clinic (107). There was no significant relationship between TSH levels and the total number of hypothyroid symptoms experienced by all patients ($P = 0.99$), and logistic regression analyses showed that clinical signs and symptoms were poor predictors of SHypo in these elderly patients (107).

A community-based cross-sectional study was recently performed on a total of 1423 non-healthcare-seeking women, aged 18–75 yr randomly recruited. Short-Form 36 (SF-36) and the Psychological General Well-being Index (PGWI) were used to evaluate health-related quality of life in subjects with SHypo defined as serum TSH above 4.0 mIU/liter. In

this study, SHypo was not associated with lower well-being or impaired health-related quality of life (108).

The presence of symptoms in patients with SHypo was evaluated in two studies. In a study by Cooper *et al.* (109), patients with SHypo had a higher prevalence of hypothyroid symptoms than age- and sex-matched euthyroid controls. However, in a study by Kong *et al.* (110) of women with SHypo, the most common hypothyroid symptoms were fatigue (83%) and weight gain (80%). At presentation, 20 women (50%) had elevated anxiety scores, and 22 (56%) had elevated scores on the General Health Questionnaire (110).

Results obtained with anxiety scores and cognitive deficiency scores in SHypo subjects are controversial (77, 92, 111–117). Impaired memory function has been reported in SHypo in small numbers of patients (111, 113), but more recent larger studies have not corroborated this observation (77, 92, 112, 114–117). For example, an interview survey of 825 Medicare subjects in New Mexico (mean age, 74.1 yr) did not reveal any differences in the age-adjusted frequency of self-reported symptoms, cognitive tests, or depression between subjects with elevated serum TSH (from 4.7 to 10 mIU/liter) and those with normal TSH concentrations (77). Also, in a prospective observational population study of 559 individuals monitored from ages 85 through 89 yr, plasma TSH levels and FT4 were not associated with disability in daily life, depressive symptoms, or cognitive function (92). The relation between neuropsychological function and SHypo (defined as serum TSH between 3.5 and 10 mIU/liter) was recently studied in 89 subjects with SHypo older than 29 yr and 154 control subjects recruited from a general health survey (115). No significant differences in cognitive function or hypothyroid symptoms were observed between patients and controls, whereas patients scored better than controls on the General Health Questionnaire (GHQ-30) for emotional function. In a survey carried out in Pomerania, which included 3790 participants with known thyroid disease, 27 subjects with SHypo did not differ from controls in their mental and physical complaints (116). However, autoimmune thyroiditis in 47 patients was associated with negative effects on health also in euthyroid subjects (116). A recent cross-sectional study of 5865 patients at least 65 yr of age with known thyroid disease (168 with SHypo defined by TSH $>$ 5.5 mIU/liter) was carried out in primary care practices in England to assess the association with cognitive function, depression, and anxiety. This study provides good evidence that SCTD is not associated with depression, anxiety, or cognition (117). In contrast, in a recent study, functional magnetic resonance imaging (MRI) was used to evaluate brain function in overt and SHypo patients in comparison with euthyroid subjects (118). This study suggested that working memory (but not other memory functions) is impaired by SHypo, and impairment is more severe in overt hypothyroidism (118).

In conclusion, the presence of symptoms in patients with SHypo remains controversial. It is difficult to distinguish euthyroid subjects from patients with SHypo using clinical symptoms. Moreover, many symptoms are nonspecific. In our opinion, symptoms of hypothyroidism are probably related to disease severity, disease duration, and individual sensitivity to thyroid hormone deficiency, which in turn depend on the sensitivity of the peripheral target organs. Age may also affect the identification of symptoms of hypothyroidism. The typical findings of hypothyroidism are less common in the elderly and, when present, are often attributed to chronic illnesses, drugs, depression, or age (119, 120). Similarly, clinical signs and symptoms are poor predictors of SHypo in the elderly; this may explain why the diagnosis of SHypo, like overt disease, may be delayed in elderly patients (Fig. 1). Symptoms and signs can also be minimal or nonspecific in young and middle-aged patients with SHypo. Furthermore, patients with SHypo identified by population screening may be more likely to be asymptomatic than those identified in clinical trials. In fact, patients with persistent SHypo or with a poor quality of life are more likely to present to a physician for thyroid function testing. The presence of specific symptoms may suggest thyroid hormone deficiency and may serve to identify patients who need thyroid function tests and to select SHypo patients who can benefit from replacement therapy. Patients who report more symptoms and more recently developed symptoms may be more likely to have overt thyroid hormone deficiency (105).

G. Cardiovascular risk in subclinical hypothyroidism

The cardiovascular system is a major target of thyroid hormone action (121, 122). Therefore, evaluation of the cardiovascular effects of thyroid hormone deficiency has shed light on the clinical significance of SHypo (121–122). Changes in cardiac hemodynamics depend on the severity of thyroid hormone deficiency, but the most frequent changes in hypothyroid patients are increased systemic vascular resistance (SVR), diastolic dysfunction, reduced systolic function, and decreased cardiac preload (121–123). All these abnormalities regress with L-T_4 replacement therapy. Hypertension, hyperlipidemia, diabetes, and cigarette smoking are major independent risk factors for cardiovascular disease (124). An increased risk for atherosclerosis is supported by autopsy and epidemiological studies in patients with thyroid hormone deficiency and may be in part explained by the hypercholesterolemia and marked increase in LDL typical of this condition (125, 126). Moreover, diastolic hypertension due to increased SVR, increased arterial stiffness and endothelial dysfunction, altered coagulability, and increased levels of C-reactive protein (CRP) may further contribute to the increased cardiovascular risk associated with overt hypothyroidism and possibly SHypo (123, 126). In this review, the cardiovascular risk in patients with SHypo will be assessed

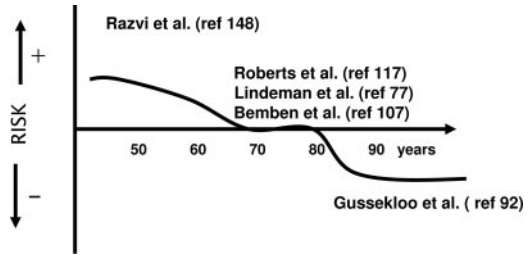

FIG. 1. Hypothetical relationship between age and effect of SHypo on symptoms, mood, and cognition. Published data suggest that the possible effects are age related.

by evaluating cardiovascular morphology and function and potential risk factors for atherosclerosis.

1. Cardiac function in SHypo. The impact of SHypo on the cardiovascular system has been evaluated by looking at diastolic function, systolic function, and exercise performance (127, 128). Left ventricular diastolic function was evaluated in seven studies by Doppler echocardiography and radionuclide ventriculography at rest and during exercise, in young and middle-aged patients with Hashimoto thyroiditis and mild but persistent TSH increases compared with euthyroid controls (129–135) (Table 3). Subclinically hypothyroid patients had a more prolonged isovolumetric relaxation time and an impaired time-to-peak filling rate (which are parameters of altered left ventricular diastolic function) than controls (129–135). As shown in Fig. 2, overt hypothyroidism can affect left ventricular diastolic function (136–139) by causing decreased expression of sarcoplasmic reticulum calcium ATPase (121, 123, 136). This leads to reduced calcium reuptake into the sarcoplasmic reticulum during diastole, resulting in impaired diastolic relaxation. A similar mechanism could impair diastolic function in patients with SHypo (129–135). This cardiac finding may be an important negative prognostic factor, because isolated left ventricular diastolic dysfunction has been associated with increased morbidity and mortality in the general population (140). Moreover, impaired left ventricular diastolic function at rest may be an important cause of exercise intolerance and may lead to diastolic heart failure in the elderly (141).

Conflicting results have been reported about systolic function at rest, evaluated by systolic time intervals, in patients with SHypo (Table 4) (131–135, 142–145). Cardiac systolic function was normal in patients with SHypo in three studies in which Weissler's method (simultaneous recording electrocardiography, carotid tracing, and phonocardiogram) was used to assess systolic function (142, 143, 145). However, impaired at-rest left ventricular function, as defined by an increased preejection period (PEP)/left ventricular ejection time (LVET) ratio, was reported in five studies using the more sensitive echocardiographic technique in SHypo patients compared with control subjects (131–135). Only Tseng *et al.* (144) did not find a significant variation in PEP and PEP/LVET by means of concurrent aortic and mitral valve echocardiography. The systolic time interval alterations reported in SHypo patients resemble those found in patients with overt disease (138, 146), although they are of a lesser magnitude. Impaired left ventricular systolic (147) and diastolic (130) function on effort were also documented by Doppler echocardiography and cardiopulmonary exercise testing in SHypo patients in comparison with euthyroid controls.

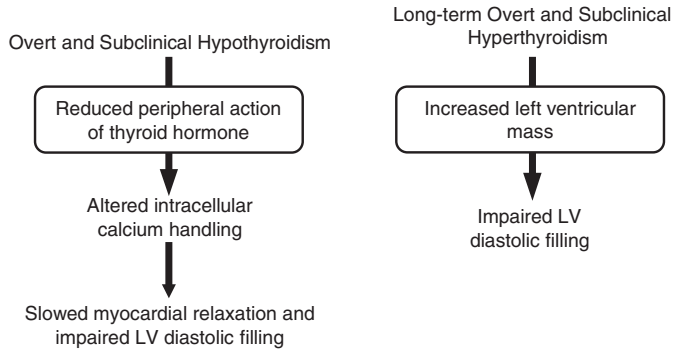

FIG. 2. Mechanism of diastolic dysfunction in overt and subclinical hypothyroidism, and in long-term overt and subclinical hyperthyroidism.

The finding of impaired systolic and diastolic function during exercise might have clinical implications in SHypo patients similar to those that occur in overt disease. In fact, reduced exercise tolerance and dyspnea on effort are the most frequent cardiovascular symptoms in overt hypothyroidism (136, 147). Unfortunately, symptoms possibly related to altered cardiac function have not been investigated systematically in patients with SHypo. Conflicting results are reported in three studies in which physical performance was investigated in SHypo patients (98, 117, 148). In one cross-sectional study, the reference scores on all eight SF-36 scales were significantly reduced in people with SHypo compared with a large UK population, and the most significantly impaired aspects of health status were vitality and role limitations due to physical problems (148).

More sophisticated techniques have recently been used to assess systolic and diastolic function and myocardial texture in patients with SHypo. Cardiac MRI (CMR), which gives high resolution, three-dimensional reconstructions, is at present the most accurate procedure with which to evaluate cardiac volumes and function. Indeed, it resolved conflicting data about systolic function in mild SHypo (149). Thirty women with SHypo (TSH range, 8.7 ± 3.7 mIU/liter) due to Hashimoto thyroiditis and 20 matched control subjects were evaluated by MRI in comparison with normal subjects. Cardiac volumes and systolic performance were significantly altered in the SHypo patients. In particular, the preload (end-

TABLE 3. Left ventricular diastolic function in patients with SHypo in comparison with euthyroid control individuals

First author, year (Ref.)	No. of patients	Age (yr)	TSH (mIU/liter)	Cardiac findings	Cardiac methods
Biondi, 1999 (129)	26	36 ± 12	8.6 ± 4.8	↑ A, ↓ E/A, ↑ IRT	Doppler echo
Di Bello, 2000 (131)	16	32 ± 12	5.3 ± 1.9	↑ A, ↔ E/A, ↑ IRT	Doppler echo
Monzani, 2001 (133)	20	33 ± 12	5.4 ± 2.4	↔ E/A, ↑ A, ↑ IRT	Doppler echo
Vitale, 2002 (132)	20	38 ± 12	10.6 ± 4.05	↔ E/A, ↑ IRT	Doppler echo
Brenta, 2003 (130)	10	50 ± 8.7	11.0 ± 4.2	↑ TPFR	Radionuclide ventriculography
Yazici, 2004 (134)	45	40 ± 7.9	8.41 ± 2.1	↑ A, ↑ IRT, ↓ E/A	Doppler echo
Aghini-Lombardi, 2006 (135)	24	35 ± 6.2	5.3 ± 1.1	↑ A, ↑ IRT, ↓ E/A	Doppler echo

Values represent mean ± SD. IRT, Isovolumic relaxation time; TPFR, time-to-peak filling rate; E/A, early-to-late transmitral peak flow velocity ratio.

P values for SHypo *vs.* control subjects: IRT, Biondi and Yazici, $P < 0.001$; Di Bello, $P < 0.04$; Monzani, $P < 0.03$; Vitale, $P < 0.005$; Aghini-Lombardi, $P < 0.01$. E/A, Biondi and Yazici, $P < 0.001$; Monzani, $P < 0.01$; Vitale, $P < 0.005$; Aghini-Lombardi, $P < 0.02$. A, Biondi, $P < 0.05$; Yazici, $P < 0.01$; Di Bello, $P < 0.01$; Monzani, $P < 0.01$; Aghini-Lombardi, $P < 0.01$. TPFR, $P < 0.001$.

TABLE 4. Left ventricular systolic function in patients with SHypo in comparison with euthyroid control individuals

First author, year (Ref.)	No. of patients	TSH (mIU/liter)	Cardiac findings	Cardiac methods
Bough, 1978 (142)	10	8.1 ≥ 50	↔PEP,↔PEP/ET	Weissler's method
Foldes, 1987 (143)	17	10.3 ± 6.34	↔PEP,↔PEP/ET	Weissler's method
Tseng, 1987 (144)	22	10.7 ± 10.3	↔PEP,↔PEP/ET	Concurrent aortic and mitral valve echo
Staub, 1992 (145)	35	<6		
	14	6–12	↔PEP,↔PEP/ET	Weissler's method
	20	>12		
Di Bello, 2000 (131)	16	5.3 ± 1.9	↑ PEP, ↑ PEP/ET	Doppler echo
Vitale, 2002 (132)	20	10.5 ± 4.05	↑ PEP, ↑ PEP/ET	Doppler echo
Monzani, 2001 (133)	20	5.4 ± 2.4	↑ PEP, ↑ PEP/ET	Doppler echo
Yazici, 2004 (134)	45	8.4 ± 2.1	↔PEP, ↑ PEP/ET	Doppler echo
Aghini-Lombardi, 2006 (135)	24	5.3 ± 1.1	↑ PEP, ↑ PEP/ET	Doppler echo

Values represent mean ± SD. ET, Ejection time; PEP, preejection period.
P values for SHypo *vs.* control subjects: PEP, Di Bello, $P < 0.03$; Vitale, $P < 0.05$; Monzani, $P < 0.02$; Aghini-Lombardi, $P < 0.05$. PEP/ET, Di Bello, $P < 0.01$; Vitale, $P < 0.05$; Monzani, $P < 0.03$; Yazici, $P < 0.05$; Aghini-Lombardi, $P < 0.02$.

diastolic volume) was significantly decreased and the afterload (SVR) was significantly increased, thereby leading to impaired cardiac performance (149).

Tissue Doppler imaging is an emerging noninvasive ultrasound tool that makes it possible to measure velocities at any point of the ventricular wall during the cardiac cycle. It is minimally affected by alterations in afterload and changes in heart rate (150). Tissue Doppler imaging revealed changes in myocardial time intervals in several segments in 20 healthy women with SHypo (TSH, 10.5 ± 4.05 mIU/liter) (132). Myocardial time intervals, evaluated as precontraction time, the precontraction time/myocardial contraction time ratio, and myocardial relaxation time, were prolonged at the level of both the posterior septum and the mitral annulus in patients with autoimmune SHypo in comparison with controls (132). These alterations were similar to those identified in patients with overt hypothyroidism (138).

Finally, ultrasonic myocardial textural analysis was used in two studies to characterize myocardial tissue in patients with SHypo (131, 133). The cyclic variation index, which is a percentage of systolic/diastolic change in mean gray levels of the interventricular septum and the left ventricular posterior wall, was lower in patients than in normal subjects. These findings are indicative of alterations in myocardial composition, which may represent early myocardial structural changes in mild thyroid deficiency.

In conclusion, the most consistent cardiac abnormality reported in patients with SHypo is impaired left ventricular diastolic function, which is characterized by slowed myocardial relaxation and impaired ventricular filling (129–135). Results concerning systolic function at rest are not consistent (131–135, 142–145); however impaired systolic function has been identified with new, more sensitive techniques (Doppler echocardiography and CMR) (131–135, 149). Only two studies have assessed systolic function and diastolic function during exercise and documented impaired cardiac performance on effort (130, 147). All the cardiovascular alterations that have been reported in patients with SHypo are similar to those observed in overt hypothyroidism. This suggests that there is a continuum in the cardiac changes that occur through mild, subclinical disease into overt hypothyroidism.

2. Vascular system and SHypo. T_3 directly affects the vascular smooth-muscle cells that promote relaxation. It also decreases SVR by increasing tissue thermogenesis and metabolic activity (151–154). Overt hypothyroidism may be a risk factor for hypertension, and reversible diastolic hypertension has been reported in 20–40% of patients with overt disease (121, 123, 151–154). An increased risk of hypertension has also been reported in some studies of patients with SHypo (155, 156). As in overt disease, three factors can contribute to systemic hypertension in SHypo: increased peripheral vascular resistance, increased arterial stiffness, and endothelial dysfunction. An increase in SVR and in mean arterial pressure was reported in some studies of normotensive patients with SHypo compared with euthyroid subjects (129, 157) but not in all (133, 135). Recently, a significant increase in SVR was reported using CMR in 30 patients with SHypo (TSH, 8.7 ± 3.7 mIU/liter) compared with 20 euthyroid controls (149). These data suggest that mild thyroid hormone deficiency might also affect vascular tone (123).

Increased central arterial stiffness appears to be an important risk factor for cardiovascular disease. Changes in arterial wall elasticity may occur before and during the early stages of atherosclerosis and may have detrimental effects on left ventricular function and coronary perfusion. Increased arterial stiffness may contribute to the development of hypertension and has been reported to be an independent risk factor for cardiovascular morbidity and mortality (158, 159).

Increased arterial stiffness can be identified from an increased augmentation of central aortic pressure and central arterial stiffness in untreated patients with overt hypothyroidism compared with age-, sex-, and BMI-matched controls (160, 161). Pulse wave analysis has also revealed increased arterial stiffness in patients with SHypo (156). Increased arterial stiffness has also been identified from increased augmentation gradient, augmentation index, and corrected augmentation index in patients with SHypo compared with controls (162). Pulse wave velocity is a direct parameter of arterial stiffness and a marker of cardiovascular risk (163, 164). The brachial-ankle pulse wave velocity is a parameter of arterial stiffening and is a good independent predictor for coronary artery disease. It has been used to investigate the risk of ischemic heart disease in overt hypothyroidism and SHypo. Both groups of subjects tended to have increased arterial wall stiffness (160, 161). Diastolic blood pressure and brachial-ankle pulse wave velocity were significantly increased in patients with SHypo (TSH, 6.9 ± 0.82 mIU/liter) compared with normal subjects (156, 165). Moreover, central

and peripheral pulse wave velocities were significantly higher in SHypo patients than in normal subjects (156, 165).

The vascular endothelium is a regulator of vascular smooth-muscle cell function and helps to maintain homeostasis and blood fluidity. Nitric oxide in the endothelium diffuses to the vascular smooth muscle and induces relaxation. Similar to what is observed in hypothyroidism, SHypo has been found to be associated with endothelial dysfunction (33, 166). High-resolution ultrasound imaging of the brachial artery showed that, compared with a control group, flow-mediated endothelium-dependent vasodilatation was significantly impaired in hypothyroid subjects with TSH levels between 4.01 and 10 mIU/liter, and greater than 10 mIU/liter (33). Taddei *et al.* (166) used the perfused forearm technique to measure the forearm blood flow response to intrabrachial acetylcholine, which is an endothelium-dependent vasodilator, at baseline and during infusion of the NO inhibitor, N^G-monomethyl-L-arginine, in SHypo patients (TSH, 7.68 ± 3.21 mIU/liter) before and after L-T_4 therapy (166). The vasodilating effect of acetylcholine was significantly reduced in patients *vs.* healthy subjects and was not affected by N^G-monomethyl-L-arginine. Endothelial dysfunction was attributed to the reduced NO availability. Recent data suggest that low-grade chronic inflammation could be responsible for endothelial dysfunction and impaired NO availability by a cyclooxygenase (COX-2)-dependent pathway, increasing oxidative stress in patients with SHypo due to Hashimoto's thyroiditis (167).

Carotid artery intima-media thickness (CIMT) can be a useful parameter in the early diagnosis of atherosclerosis and coronary heart disease. Increased CIMT has been documented in SHypo (168, 169). Patients with SHypo had higher TC, LDL-C, and apolipoprotein (Apo) B levels and higher mean intima-media thickness (IMT) values compared with age- and sex-matched controls. Moreover, mean IMT was positively related to age, TSH, and LDL-C (168).

Myocardial functional reserve, assessed by iv dobutamine, did not differ between subjects with SHypo and controls and remained unaltered after treatment (162). There were no differences in resting global, regional left ventricular function, or regional myocardial velocities during maximal dobutamine stress between SHypo patients and controls, or in patients treated with replacement therapy compared with baseline values (162). However, in a recent study, coronary flow reserve was lower in subclinical and overt hypothyroidism than in euthyroid subjects (170).

In conclusion, on the basis of the data available, SHypo could impair vascular function by inducing an increase in SVR and arterial stiffness and by altering endothelial function, thereby potentially increasing the risk of atherosclerosis and coronary artery disease.

3. SHypo and lipid profile. The relationship between SHypo and serum lipids remains controversial (126, 171). In several cross-sectional studies, SHypo was found to be associated with a variable and somewhat inconsistent increase in TC and in LDL-C (40, 77, 172–176), higher plasma oxidized LDL-C levels (177), and inconsistent changes in serum levels of HDL-C (145, 155, 168, 172, 173, 175, 178–190). Not unexpectedly, the lipid pattern is more abnormal in SHypo individuals with serum TSH greater than 10 mIU/liter (77, 145, 173, 178, 181–183), and it is also more deranged in those who smoke (177, 183, 191). Moreover, in a group of healthy euthyroid subjects, Bakker *et al.* (191) found a strong, positive relationship between TSH and LDL-C in insulin-resistant subjects, but not in insulin-sensitive subjects.

The association between SHypo and serum TC and LDL-C has been investigated in several large population-based studies. In the Whickham Survey, SHypo was not related to hyperlipidemia (174). In the NHANES III, mean cholesterol levels and rates of elevated cholesterol levels were higher in people with SHypo (TSH, 6.7–14.9 mIU/liter) than in euthyroid controls (TSH, 0.36–6.7 mIU/liter); there were no differences in LDL or HDL levels (192). However, when adjusted for age, race, sex, and the use of lipid-lowering drugs, SHypo was not related to increased cholesterol levels (192). In another study, there was no apparent relationship in subjects with SHypo between serum concentrations of TSH ranging from 4.0 to 49.0 mIU/ml and concentrations of LDL-C (186). In the Rotterdam Study, TC was lower in women with SHypo than in euthyroid women (193). Similar data were reported in the Nagasaki study (194). In the New Mexico Elder Health survey, there were no differences in TC, HDL-C, or triglycerides between patients with a serum TSH level below 4.6 mIU/liter and those with a serum TSH level between 4.7 and 10 mIU/liter (77). The levels of LDL-C and HDL-C were higher among women with serum TSH greater than 10 mIU/liter than in euthyroid women, although the difference was not significant (77). In the Busselton study, serum TC was significantly higher in subjects with SHypo than in euthyroid subjects, but the difference was barely significant after adjustment for age and sex (195). Moreover, LDL-C was significantly increased in subjects with mild SHypo and TSH levels of at least 10 mIU/liter. In a Danish study, SHypo (TSH, 3.70 mIU/liter) was associated with a higher concentration of triglycerides and CRP (196).

In a large population-based study (2799 adults aged 70–79 yr), TSH levels were stratified to establish a cutoff for the relationship between TSH and serum lipids (197). A serum TSH level above 5.5 mIU/liter was associated with a cholesterol increase of 0.23 mmol/liter (10 mg/dl). In a cross-sectional study of middle-aged patients, Bindels *et al.* (198) estimated that, after correction for age, an increase of 1 mIU/liter in serum TSH was associated with a rise in serum TC of 0.09 mmol/liter (3.5 mg/dl) in women and 0.16 mmol/liter (6.2 mg/dl) in men. They estimated that approximately 0.5 mmol/liter (~20 mg/dl) of serum TC could be attributed to SHypo. Bauer *et al.* (172) evaluated the association of TSH with serum lipids in an unselected population of older women. After multiple adjustment, LDL-C was 13% higher and HDL-C was 12% higher in women with elevated TSH (TSH > 5.5 mIU/liter) *vs.* women with normal TSH. The LDL-C to HDL-C ratio was 29% greater among women with elevated TSH. Women with multiple lipid abnormalities were twice as likely to have increased TSH levels.

In conclusion, there are conflicting results about lipid pattern and SHypo. This might reflect differences in the population studied (*e.g.*, cause of SHypo, duration of thyroid dysfunction, TSH levels), as well as differences in age, gen-

der, and ethnicity of the subjects tested (199). In addition, smoking and insulin resistance may play a role in mediating the effects of mild hypothyroidism on serum lipids (183, 191, 199).

4. Emerging cardiovascular risk factors for atherosclerosis. "Nontraditional" blood markers for atherosclerosis risk, such as homocysteine CRP, fibrinogen, factor VIII, von Willebrand factor (vWF), and lipoprotein (a), may be associated with an increased risk of coronary heart disease (200–205). Serum lipoprotein (a) levels are mainly under genetic control and are associated with increased risk of both atherosclerosis and thrombogenesis. This lipoprotein is similar to LDL in its lipid composition, but it contains an additional glycoprotein, designated Apo A, which is linked to Apo B by disulfide bridges. Lipoprotein (a) has a striking homology to plasminogen. Studies on the association between lipoprotein (a) and SHypo have generally yielded consistently negative results (172, 177, 182, 184, 188, 189). Lipoprotein (a) was found to be increased only in patients with SHypo with a TSH value above 12 mIU/liter (182, 206), and in postmenopausal women with SHypo regardless of their serum TSH value (185). The finding that a family history of chronic heart disease (CHD) and/or diabetes was significantly associated with an elevated level of lipoprotein (a) suggested that the increase was due to a genetic effect rather than to a reduced thyroid hormone concentration (189). Similarly, homocysteine levels have not been shown to differ between individuals with SHypo and euthyroid controls in some case-control studies (155, 168, 190). Hence, total homocysteine does not appear to contribute to the potential increased risk of atherosclerotic disease and myocardial infarction in subclinical hypothyroid patients. In a cross-sectional study (New Mexico Elder Health Survey) of a randomly selected sample of Medicare recipients (age $\geq$ 65 yr), there was no significant difference in serum homocysteine concentrations between the 112 participants with SHypo (groups 2 and 3) and the 643 participants with TSH values no greater than 4.6 mIU/liter (group 1) after adjusting for differences in gender, ethnicity, age, and serum concentrations of folate, vitamin B_{12}, and creatinine (207). Only participants with the highest TSH levels (>10 mIU/ml) (group 3) had a significantly higher prevalence of coronary heart disease when compared with group 1 participants ($P = 0.007$). No consistent significant differences in the prevalence of CHD or in the CHD risk factors examined were observed when all participants with SHypo (groups 2 and 3) were compared with group 1 participants.

Patients with thyroid diseases have abnormalities of blood coagulation that may contribute to the high risk for cardiovascular disease (208). Both increased and decreased platelet adhesiveness have been reported in hypothyroidism (209, 210). Alterations in coagulation parameters have been reported in patients with SHypo (Table 5). The degree of hypothyroidism may influence coagulation parameters. In a study that compared moderate (TSH, 10–50 mIU/liter) and severe hypothyroidism (TSH, >50 mIU/liter) with the euthyroid state, women with moderate hypothyroidism had decreased fibrinolytic activity with lower D dimer levels, higher α 2 antiplasmin activities, and higher levels of tissue plasminogen activator inhibitor antigen (209). Moreover, factor VII activity and the factor VII activity:factor VII antigen ratio were significantly increased in women with SHypo (TSH, >6 mIU/liter) *vs.* euthyroid controls, whereas there were no differences in vWF or in the other hemostatic and lipid variables tested (211). This reflects activated factor VII and might indicate a hypercoagulable state in SHypo. Canturk *et al.* (212) found increased levels of fibrinogen, plasminogen activator inhibitor antigen, and factor VII and decreased antithrombin III activity in SHypo patients (TSH level, 8.9 mIU/liter) compared with controls. In another study, factor VIII and vWF activities were lower ($P < 0.01$) in patients with SHypo than in controls (213). The global fibrinolytic capacity was significantly lower in patients with SHypo than in controls ($P < 0.002$) in the study by Guldiken *et al*. (214). Finally, in the recent fifth Tromsø study, an epidemiological health survey, 83 subjects fulfilled the criteria for SHypo (TSH level, 3.5–10.0 mIU/liter), and their blood samples were analyzed for the hemostatic factors and compared with 249 age- and sex-matched control subjects with serum TSH in the range 0.50–3.49 mIU/liter. There were no statistically significant differences between the SHypo group and the controls regarding the hemostatic factors. However, the factor VIIa levels were 10% lower in the SHypo group than in the controls ($P = 0.055$ after correction for multiple comparison). Moreover, in the linear regression model serum TSH was a significant and negative predictor of the factor VIIa level (215). On the whole, the above data support the hypothesis that alterations in coagulation parameters might play a role in the potential development of atherosclerosis in patients with SHypo. The clinical importance of this finding needs further study.

CRP is a strong predictor of cardiovascular risk. There is disagreement about whether or not abnormalities of CRP occur in patients with SHypo. CRP levels were significantly higher in subclinical hypothyroid patients than in controls in three studies (190, 196, 216). SHypo was associated with higher concentrations of triglycerides and CRP in the study by Kvetny *et al*. (196) and was a predictor of cardiovascular disease in males below 50 yr of age, with an OR of 3.4 for developing cardiovascular disease compared with euthyroid age-matched males. Moreover, in the study by Tuzcu *et al.*

TABLE 5. Hemostatic profile in patients with SHypo in comparison with euthyroid control individuals

First author, year (Ref.)	TSH (mIU/liter)	SHypo
Chadarevian, 2001 (209)	10–50	↓ D Dimer, ↑ α2 antiplasmin activities, ↑ tissue plasminogen activator inhibitor antigen
Muller, 2001 (211)	>6	↑ Factor VII:C, ↔ vWF, ↑ Factor VII:C/Factor VII:Ag
Canturk, 2003 (212)	>8.9	↑ Fibrinogen, ↑ Plasminogen activator inhibitor antigen, ↑ Factor VII, ↓ antithrombin III
Gullu, 2005 (213)	5–10	↓ Factor VIII, ↓ vWF
Guldiken, 2005 (214)	7.3 ± 2.2	↓ Global fibrinolytic capacity
Jorde, 2006 (215)	3.5–10.0	↓ FVIIa

(216), patients with SHypo had increased levels of both high sensitive CRP (hsCRP) and fasting insulin *vs.* the control group, and there was a positive correlation between hsCRP levels and insulin levels in patients with SHypo (216). However, homeostasis model of assessment-insulin resistance [fasting insulin (μIU/ml) × fasting glucose (mmol/liter)/22.5] values were not significantly different *vs.* controls. This finding prompted the suggestion that the elevated hsCRP level, and hence low grade inflammation, could be associated with fasting hyperinsulinemia before insulin resistance becomes evident in patients with SHypo (216).

In contrast, CRP did not appear to contribute to the increased risk for coronary heart disease in subclinical hypothyroid patients reported in other studies (217, 218). In a large population-based sample taken from the NHANES, hsCRP levels were similar in patients with SHypo and euthyroid individuals (219).

Ozcan *et al.* (220) recently evaluated all these "new" cardiovascular risk factors in 84 women with SHypo and a mean serum TSH of 9.3 mIU/liter. TC, LDL-C, hsCRP, asymmetric dimethylarginine, and L-arginine levels were significantly higher in patients than in controls, whereas nitric oxide levels were lower.

In conclusion, data on a potential association of SHypo with such "nontraditional" cardiovascular risk factors are not consistent. Some studies support an increase in CRP and alterations in coagulation parameters (190, 196, 209, 211–214, 215, 216, 220) in SHypo patients compared with euthyroid age-matched subjects. Although homocysteine is an important cardiovascular risk factor in patients with overt hypothyroidism, it does not seem to have a role in SHypo patients (155, 168, 190, 207).

5. Epidemiological studies. The data from case-control and cross-sectional studies are controversial with respect to the association between SHypo and cardiovascular disease (221–224). In an early study of 945 consecutive hospitalized patients, women with a TSH level greater than 4 mIU/liter had a significantly increased prevalence of coronary heart disease (222). In a cross-sectional study (New Mexico Elder Health Survey) of a randomly selected sample of Medicare recipients (age ≥ 65 yr), only subjects with the highest TSH levels (>10 mIU/liter) had a significantly higher prevalence of coronary heart disease (77). SHypo has also been associated with a high prevalence of dyslipidemia and a high prevalence of coronary heart disease in elderly men and women (mean age, 75 ± 9 yr) (224). However, a Finnish group found no association between SHypo and coronary heart disease in men and women (225). Peripheral arterial disease was associated with SHypo in a case-control study of elderly women (226).

In the Whickham survey of 2779 randomly selected men and women 18 yr old and above, there was no association between autoimmune thyroid disease at study entry and subsequent death from ischemic heart disease (227). The assessment of ischemic heart disease was based on a verbally administered standardized World Health Organization pain-on-effort questionnaire, a personal history of angina or myocardial infarction, and standard 12-lead electrocardiogram (ECG) evaluation. In this 20-yr cohort study, autoimmune thyroid disease was not associated with coronary disease. Autoimmune thyroid disease was defined as treated hypothyroidism, positive antibodies, or elevated serum TSH, without a separate analysis of individuals with elevated serum TSH levels (228).

In the large cross-sectional Rotterdam study of 1149 women 55 yr or older, SHypo (defined as TSH > 4.0 mIU/liter) was present in 10.8% of participants (124 women), and its association with atherosclerosis and myocardial infarction was investigated (193). Aortic atherosclerosis was assessed from calcified deposits in the abdominal aorta on a radiographic film of the lumbar spine (193). Myocardial infarction was assessed by self-report and by analysis of standard 12-lead ECGs. Women with SHypo were found to have an increased risk of atherosclerosis (OR 1.7, 95% CI 1.1–2.6) and a history of myocardial infarction (OR 2.3, 95% CI 1.3–4.0). There was no association between TA itself and cardiovascular disease, but patients with both mild TSH elevation and positive antibodies had an increased relative risk. The risk of myocardial infarction was not significantly increased during an average follow-up of 4.6 yr (193).

Parle *et al.* (229) carried out a 10-yr cohort study of 1191 men and women 60 yr or older. The causes of death were compared with age-specific, sex-specific, and year-specific data for England and Wales. In this study, SHypo (defined as TSH > 5.0 mIU/liter with a prevalence of 10.8%) (94 subjects) was not associated with death from circulatory disease during the 10-yr follow-up. However, 40% of individuals with SHypo developed overt hypothyroidism during follow-up and began T_4 replacement therapy.

In a cohort of atomic bomb survivors from Nakasaki (2550 men and women 40 yr or older; mean age, 58.5 yr), SHypo (defined as TSH > 5.0 mIU/liter with a prevalence of 10.2%) (257 subjects) was associated with ischemic heart disease and increased all-cause mortality in the cross-sectional analysis, but only in men (194). The prevalence of ischemic heart disease was independent of such coronary risk factors as blood pressure, BMI, TC level, smoking status, and presence of diabetes mellitus. There was no association between SHypo and cerebrovascular disease, and the presence of thyroid antibodies did not affect the association between SHypo and ischemic heart disease. In the longitudinal follow-up study, all-cause mortality was increased at 6 yr only in men, although the specific causes of death were not determined. However, mortality was not increased at the 10-yr mark.

In the Leiden prospective cohort study of subjects aged 85 yr, SHypo was present in 30 patients, and in the 21 individuals reassessed at age 88 yr it was associated with greater longevity and a decreased risk of death from cardiovascular disease during the 4-yr follow-up, and this was attributed to a lower metabolic rate (92). Individuals with overt hypothyroidism and SHypo had lower all-cause and cardiovascular mortality than clinically euthyroid individuals, although serum cholesterol levels were higher.

The community-based study carried out in Busselton, Western Australia, evaluated SHypo as a risk factor for cardiovascular disease and found that this condition was an independent predictor of coronary heart disease in the cross-sectional and longitudinal analysis (38). The study included

1063 men and 1045 women (mean age, 50 yr; range, 17–89 yr), and the prevalence of SHypo was 5.6% (119 subjects). Euthyroid subjects were those with a serum TSH of 0.4 to 2.0 mIU/liter, and patients with SHypo were divided into those with a serum TSH level of 4–10.0 mIU/liter and those with a serum TSH greater than 10 mIU/liter. In the cross-sectional analysis, the prevalence of coronary heart disease was significantly higher in patients with SHypo and serum TSH greater than 10 mIU/liter *vs.* euthyroid subjects (OR 1.8; 95% CI, 1.0–3.1; $P = 0.04$), after adjustment for age, gender, cardiovascular risk factors, and self-reported thyroid disease or goiter. The association with coronary heart disease was significant in subjects with a TSH level greater than 10 mIU/liter, but not in patients with mild to moderate SHypo (TSH 4–10 mIU/liter). In the longitudinal analysis (20 yr of follow-up of 101 subjects with SHypo), the risk for coronary heart disease was significantly increased in subjects with SHypo after adjustment for age and gender (21 cardiovascular deaths compared with 9.5 expected, and 33 coronary heart disease events compared with 14.7 expected). The increased risk for coronary events associated with SHypo was found in subjects with a serum TSH level of 10 mIU/liter or less as well as in those with a serum TSH greater than 10 mIU/liter. The risk remained significant after adjustment for standard cardiovascular risk factors. There was no increased risk of death from cardiovascular disease in patients with SHypo of any degree (38). In a cross-sectional study of 1212 men and women aged 20–69 yr carried out in Denmark, SHypo defined by TSH greater than 2.8 mIU/liter, TSH was a predictor of cardiovascular disease, but only in subjects younger than 50 yr (196).

In 1989–1990, 3233 U.S. community-dwelling individuals aged 65 yr or older were enrolled in the Cardiovascular Health Study, a population-based longitudinal study of risk factors for the development of CVD in 5888 adults (230). Eighty-two percent of participants (n = 2639) had normal thyroid function, 15% (n = 496) had SHypo, 1.6% (n = 51) had overt hypothyroidism, and 1.5% (n = 47) had SHyper. SHypo was defined as a TSH concentration above 4.50 mIU/liter and below 20 mIU/liter and a normal FT4 concentration. L-T_4 replacement therapy was started during the follow-up in 142 subjects with SHypo and in 31 with overt hypothyroidism. Data were adjusted for the use of thyroid hormone medication. There were no differences in the incidence of coronary heart disease, cerebrovascular disease, cardiovascular disease, or all-cause death between the euthyroid and subclinical or overt hypothyroid groups either in the cross-sectional survey or in the longitudinal component of this study. Moreover, there were no differences in serum cholesterol concentrations, lipoprotein (a), CRP, or fasting insulin and glucose concentration between individuals with SHypo and those with normal thyroid function.

Congestive heart failure has also been linked to SHypo in several studies. Rodondi *et al.* (231) assessed the risk of SHypo (defined as a TSH level of 4.5 mIU/liter or greater) on heart failure, coronary heart disease, stroke, peripheral arterial disease, and cardiovascular-related and total mortality. A total of 2730 men and women, aged 70–79 yr, were evaluated and classified according to TSH levels (4.5–6.9, 7.0–9.9, and ≥ 10 mIU/liter). SHypo was present in 12.4% of subjects (338 subjects), and about 68% of all participants had mild disease (TSH, 4.5–6.9 mIU/liter). At study entry, no association was found between SHypo of any degree and the prevalence of cardiovascular disease, heart failure, and coronary heart disease. During the 4-yr follow-up, 178 subjects had heart failure. Congestive heart failure was evaluated by a panel of clinicians based on symptoms, signs, chest x-ray, and echocardiographic findings. SHypo was associated with an increased risk of congestive heart failure (CHF) among older adults with a TSH level of 7.0 mIU/liter or greater. Congestive heart failure events occurred more frequently among subjects with a moderate or severe TSH increase (TSH, 7.0–9.9 and ≥10 mIU/liter, respectively; 35.0 *vs.* 16.5 per 1000 person-years; $P = 0.06$), but rates were similar to controls among those with serum TSH levels between 4.5 and 6.9 mIU/liter ($P = 0.71$). When TSH was used as a continuous variable, each SD increase of 4.0 mIU/liter was associated with a 30% increase in CHF events (95% CI, 8–55%; $P = 0.04$). SHypo was not associated with coronary heart disease events, stroke, peripheral arterial disease, cardiovascular mortality, or total mortality, despite significant higher cholesterol levels. Because no other prospective study has assessed the risk of CHF events in subjects with SHypo, other large prospective studies are required to determine whether SHypo causes or worsens preexisting heart failure.

An increased risk of CHF in patients with SHypo was also identified in two small cross-sectional studies (232, 233). In one study, 8 of 31 (26%) patients with CHF had a serum TSH level greater than 3.6 mIU/liter with normal T_4, suggesting the possibility of a significant prevalence of SHypo in patients with moderate-to-severe CHF (232). In the other study, 97% of patients with CHF had both SHypo and morphological thyroid abnormalities (233). These studies were not prospective, nor did they include a control group without CHF.

Although SHypo has been associated with signs of aortic and coronary atherosclerosis, only a few studies evaluated SHypo as a risk factor for atherothrombotic stroke (194, 230, 231, 234). Although the Classification of Cerebrovascular Disease III study found that hypothyroidism was a risk factor for stroke (235), other studies have not found an association between SHypo and stroke (194, 230, 231). In a recent report, SHypo (TSH < 10 mIU/liter) was associated with a significantly better outcome in patients with acute stroke (236). The protective effect might be attributable to the reduced adrenergic tone (237) or other unknown factors.

The potential cardiovascular risk in SHypo patients is an important factor that affects decisions about the screening and treatment of these patients. A recent meta-analysis evaluated the association of SHypo with all-cause and circulatory mortality (238). Not all possible relevant confounders for the association between SHypo and mortality were considered in each of the prospective cohort studies. In fact, associated atherosclerotic risk factors were evaluated only in few studies (38, 227, 230, 231), and baseline coronary artery disease was assessed in only two studies (38, 230). Moreover, two other studies (92, 194) involved selected populations (atomic bomb survivors and 85-yr-old individuals), thereby limiting the generalizability of the findings. Consequently, the authors of the meta-analysis concluded that the current evidence for a causal relation of SHypo with mortality is weak

and should not be used to decide whether or not to treat SHypo patients (238).

In conclusion, there are major discrepancies in epidemiological data about cardiovascular risk in SHypo (Table 6). This may be due to differences in the populations studied in terms of age, sex, race/ethnicity, life style, the TSH range that defines SHypo, methods of evaluation of cardiovascular disease, differences in adjustments for known risk factors for cardiovascular disease, and duration of follow-up. Few studies stratified the analysis by TSH levels. Only one cross-sectional study included a subgroup analysis by age and found that the risk of CHD associated with SHypo was higher and statistically significant only in subjects younger than 50 yr (196). Furthermore, not all epidemiological studies included follow-up data on thyroid function, and in other studies some patients were treated with thyroid hormone during follow-up. Only one study (194) reported increased all-cause mortality in a male subpopulation of SHypo patients, whereas one study reported decreased all-cause mortality in very elderly SHypo subjects (92). The risk of coronary disease was increased in SHypo in the cross-sectional analysis in the Rotterdam study (193) and in the cross-sectional and longitudinal analysis in the Busselton study (38). An increased risk of CHF was found in the only study in which it was evaluated (231). If there is an excess risk of coronary artery disease in SHypo, the causes remain unknown because the risk was not explained by an excess of traditional risk factors (174, 193–195, 230, 231). However, the possibility of an increased prevalence of nontraditional risk factors (endothelial dysfunction, CRP, and alterations in coagulation parameters) in SHypo remains to be clarified.

H. Subclinical hypothyroidism and neuromuscular dysfunction

Hypothyroidism may induce a wide spectrum of alterations in neuromuscular function, and muscle-related symptoms are frequent in patients with hypothyroidism. The mechanism underlying abnormal muscle dysfunction is only partly known. Impaired glycogenolysis (239, 240), alterations in myosin heavy chain expression (241), and reduced mitochondrial activity have been implicated in this process (242, 243). The amplitude of the stapedial reflex, a biological parameter that reflects neuromuscular status, was abnormal in patients with subclinical and overt hypothyroidism (244). On the other hand, distal motor latencies, motor and sensory amplitudes, and nerve conduction velocities were not abnormal in patients with mild thyroid hormone deficiency (245). Similarly, no abnormalities of peripheral nerves or brainstem auditory evoked potentials were identified in patients with SHypo of short duration (246). Conflicting data have been reported about the increase of serum creatine kinase and serum myoglobin levels in patients with SHypo (145, 247–249). A positive correlation between creatine kinase and TSH and a negative correlation between creatine kinase and FT3 and FT4 have been reported in overt and subclinical hypothyroid patients, (248). Monzani *et al.* (250) determined skeletal muscle lactate and pyruvate production in the resting state and during dynamic arm exercise in 12 patients with SHypo who complained of mild neuromuscular symptoms.

TABLE 6. Epidemiological evidence for the association between SHypo and cardiovascular risk

First author, year (Ref.)	No. of patients	Sex	TSH	Age (yr)	Follow-up (yr)	Cardiovascular risk
Vanderpump, 1996 (227)	2779	W and M	ATD	≥18	20	No association of ATD with coronary disease. No increased circulatory or all-cause mortality.
Hak, 2000 (193)	1149 (124 SHypo)	W	>4.0	≥55	4.6	Risk of atherosclerosis. Risk of MI only in cross-sectional analysis.
Parle, 2001 (229)	1191 (94 SHypo)	W and M	>5.0	≥60	10	No association with death from circulatory disease.
Imaizumi, 2004 (194)	2550 (257 SHypo)	W and M	>5.0	≥40	10	Increased mortality from all causes at longitudinal analysis in yr 3–6 only in men, but not at 10 yr. Increased risk of IHD only in the baseline cross-sectional analysis.
Gussekloo, 2004 (92)	599 (30 SHypo)	W and M	4–8 in 25, ≥10 in 5	≥85	4	Decreased risk of death
Walsh, 2005 (38)	2108 (119 SHypo)	W and M	0.4–2, 2.0–4, <10, >10	17–89	20	Risk for coronary events in subjects with serum TSH levels of 10 mIU/liter or less and greater than 10. No increased risk of death from cardiovascular disease.
Rodondi, 2005 (231)	2730 (338 SHypo)	W and M	4.5–6.9, 7–9.9, ≥ 10	70–79	4	Increased risk of CHF in patients with TSH > 7 mIU/liter. No increased cardiovascular or total mortality.
Cappola, 2006 (230)	5888 (496 SHypo)	W and M	≥4.5	≥65	13	SHypo was not associated with cardiovascular disorders or mortality.

ATD, Autoimmune thyroid disease; MI, myocardial infarction; IHD, ischemic heart disease; W, women; M, men; CHF, congestive heart failure.

Blood lactate and pyruvate levels did not differ between patients and controls at rest. However, the mean lactate level and the mean lactate increment were significantly higher in patients with SHypo than in controls during exercise. This finding is consistent with impaired mitochondrial oxidative function. Moreover, the mean increment in blood lactate during exercise was positively related to the duration of SHypo, but not to the serum levels of TSH, FT3, and FT4. There was no difference in blood pyruvate concentration during exercise. This study suggests that muscle energy metabolism may be impaired in SHypo in proportion to disease duration.

Finally, in a recent study by the same authors, muscle metabolism and the response to exercise were significantly impaired in SHypo. Exercise tolerance and both maximal power output and maximum oxygen uptake (VO_2) were lower in SHypo, and respiratory quotient increments were significantly higher in patients than in controls (251). Blood lactate and pyruvate and their ratio increased with a steeper slope in patients *vs.* controls. Resting plasma free fatty acid and blood glycerol levels were significantly higher in patients at baseline and during exercise and recovery (251).

I. Effects of replacement therapy

1. Effects of treatment on disease progression. Treatment of goiter in patients with Hashimoto's thyroiditis with L-T_4 is usually recommended with the aim of decreasing thyroid size. However, thus far only three uncontrolled studies have evaluated the effect of this treatment on thyroid volume in goitrous subjects with overt hypothyroidism and SHypo induced by Hashimoto thyroiditis (252, 253, 254). In one study, treatment with L-T_4 for 3 yr induced a 32% reduction in thyroid volume in adults after L-T_4 replacement evaluated by ultrasound, although TPOAb remained unchanged (252). Similarly, in another study a significant decrease in the thyroid volume (decreased 80.9% % of initial volume; $P < 0.01$) was found in 77% (10 of 13) of SHypo adult patients with Hashimoto's thyroiditis after replacement therapy with L-T_4 (253). In the third study, L-T_4 treatment, for a median 2.8 yr, was effective in reducing thyroid volume in 90 pediatric patients with Hashimoto's thyroiditis, especially in those with hypothyroidism (254). In the latter study, median thyroid volume was reduced in euthyroid patients (−0.4 SD score; $P < 0.001$), subclinically hypothyroid (−1.4 SD score; $P < 0.001$), and overtly hypothyroid (−1.8 SD score; $P < 0.002$) children with autoimmune thyroiditis (254).

Serum TPO and other thyroid antibodies may decrease during treatment with L-T_4 in patients with Hashimoto thyroiditis or idiopathic myxedema (255). In hypothyroid patients with TSH receptor antibodies, treatment with L-T_4 for 4 to 8 yr was associated with disappearance of these antibodies in 71% of patients and euthyroidism in 50% after L-T_4 discontinuation (256). In an unselected group of patients, the degree of hypothyroidism worsened in 20 patients, remained unchanged in 40, and improved in 19 at least 1 yr after L-T_4 withdrawal. A large goiter and high TSH levels at the time of diagnosis, associated with a familial incidence of thyroid disease, were related to an increased likelihood of recovery of normal thyroid function (257). In a group of children with Hashimoto's thyroiditis, euthyroidism was obtained after L-T_4 withdrawal in some patients with goiter, whereas hypothyroidism was irreversible in children with atrophic thyroiditis (258).

2. Effects of replacement therapy on symptoms and signs. Eight placebo-controlled studies have assessed the effects of L-T_4 replacement therapy on symptoms and signs, quality of life, and psychometric tests in subclinical hypothyroid patients (97, 109, 110, 115, 249, 259–261). The double-blind placebo-controlled study carried out by Cooper *et al.* (109) reported a higher prevalence of specific symptoms and signs assessed with the Billewicz clinical hypothyroidism scale in 33 subclinical hypothyroid patients aged 32–78 yr, with a mean baseline TSH of 10.8 mIU/liter (TSH range, 3.6–55.3 mIU/liter) than in euthyroid controls. The study population was selected from a large cohort of women enrolled in a follow-up study of patients treated for hyperthyroidism. The SHypo patients had more hypothyroid symptoms than the 20 euthyroid controls. One year after the study onset, the symptom score improved significantly (by 2.1 points; individual scores ranged from −5 to +9) in patients treated with replacement doses of L-T_4 (between 0.05 and 0.125 mg); their TSH level was 2.6 ± 0.5 mIU/liter. In contrast, the mean symptom score decreased by 1.2 points in the placebo group (TSH 14.7 ± 3.3 mIU/liter). The symptom score improved in 50% of the L-T_4-treated group *vs.* about 25% of the placebo group. Similarly, in another double-blind crossover 12-month study of 20 women aged 51–73 yr with SHypo (TSH concentration between 4 and 15 mIU/liter with ΔTSH above 30 mIU/liter after TRH), neuropsychometric parameters improved after 6 months of replacement L-T_4 therapy in patients with serum TSH levels between 4.8 and 9.9 mIU/liter (249). However, a fixed L-T_4 dosage was used in this study, with a final L-T_4 daily dose of 0.15 mg. In a double-blind placebo-controlled study of 37 patients older than 55 yr, Jaeschke *et al.* (259) reported a significant improvement in memory scores but not in overall health-related quality of life.

Meier *et al.* (260) evaluated 66 women, aged 18–75 yr, with SHypo (TSH 11.7 ± 0.8 mIU/liter) due to thyroiditis or a history of Graves' disease. An improvement in two symptom scores (the Billewicz and Zulewski scores) was observed after 48 wk of replacement therapy *vs.* baseline values. However, the comparison of the mean treatment effects between the two treatment groups (placebo group and the T_4 group) did not reach the level of significance (Billewicz score, $P = 0.31$; Zulewski scores, $P = 0.53$). An improvement in symptom score was seen only in patients with pretreatment TSH values higher than 12 mIU/liter and was not significant in patients with pretreatment TSH values lower than 12 mIU/liter.

Kong *et al.* (110) evaluated 40 women (mean age, 49 yr) with SHypo and serum TSH between 5 and 10 mIU/liter randomly assigned to receive L-T_4 or placebo for 6 months. The Hospital Anxiety and Depression scores and the General Health Questionnaire score did not change significantly after placebo or L-T_4, which suggests that replacement therapy had no benefit in women with SHypo. As absolute scores, anxiety scores in the L-T_4-treated group improved in 50%, were unchanged in 10%, and worsened in 40%. In the placebo

group, there was improvement, no change, and worsening in 50, 43, and 7%, respectively. Depression scores in the T_4 group improved in 65%, were unchanged in 25%, and were worse in 10% compared with 64, 7, and 29%, respectively, in the placebo group. The General Health Questionnaire scores in the T_4 group improved in 60%, were unchanged in 10%, and were worse in 6%, compared with 92, 0, and 8%, respectively, in the placebo group. However, serum TSH was measured only once, so it is possible that some patients had a mild transient TSH increase and not persistent SHypo. In fact, after 6 months of treatment, women in the placebo group showed a trend toward spontaneous normalization of thyroid function (mean baseline ± SD, TSH 7.3 ± 1.6 mIU/liter; mean change from baseline, −1.7 ± 2.0 mIU/liter). Moreover, a fixed L-T_4 dose was given (50 or 100 μg/d), and TSH did not normalize in all L-T_4 treated patients but remained at the upper limit of normal range with some patients benefiting more from treatment than others (baseline TSH value, 8.9 ± 1.5 mIU/liter; change from baseline, −4.6 ± 2.3 mIU/liter).

In the Tromso study of 89 subjects (TSH 5.57 ± 1.68 mIU/liter), the relation between neuropsychological function and SHypo was investigated by using 14 tests of cognitive function, the Beck Depression Inventory, General Health Questionnaire, and a questionnaire on hypothyroid symptoms (115). In this double-blind placebo-controlled study with T_4 given for 1 yr, there was no significant difference between T_4 therapy and placebo as regards cognitive function or depression (115).

In a recent randomized double-blind placebo crossover study, quality of life was assessed in the largest number of patients to date (100 patients; mean age, 53 ± 12 yr; range, 18–80 yr) with SHypo defined by TSH greater than 4 mIU/liter (261). In this study, all subscales of the SF35-version 2 (apart from the emotional item) tended toward improvement after replacement therapy with L-T_4, although none reached statistical significance after correction for multiple comparisons. Interestingly, in this study there was a trend toward improvement of sex life, which was attributed to the improvement in tiredness. However, in this study, L-T_4 was administered for a short period (3 months) and at a fixed dosage (100 μg/d), and 10% of L-T_4 subjects had subnormal serum TSH values at the end of the treatment period. In another study, L-T_4 was no more effective than placebo in improving cognitive function and psychological well-being in patients with symptoms of hypothyroidism whose thyroid function tests were within reference range (97).

In summary, conflicting results emerge from these double-blind placebo-controlled studies on the improvement of symptoms after L-T_4 therapy in SHypo patients. This is probably due to differences in the selection of patients in terms of etiology of the disease, age of patients evaluated, and TSH level at the baseline evaluation. Moreover, there are important differences in the study design in terms of duration of therapy, L-T_4 dosage, and differences in the scores used to assess the symptoms. In addition, in some studies, SHypo may not have been persistent in the placebo group, and in other studies either euthyroidism was not reached with replacement therapy or some patients were inadvertently overtreated (this is particularly true for studies in which a fixed dose of L-T_4 was used).

3. Effects of replacement therapy on cardiac function. Diastolic function improved in all studies in which it was evaluated after replacement therapy (129, 130, 133, 134); two studies were double-blind placebo-controlled investigations (133, 134) (Table 7). In the first double-blind placebo-controlled study, there was a decrease in isovolumic relaxation time and late transmitral flow velocity and a significantly improved early-to-late transmitral peak flow velocity ratio (E/A) after 1 yr of L-T_4 replacement therapy (133). These results were confirmed in the second double-blind placebo-controlled study, which also reported no significant change in left ventricular morphology (134). In one study, diastolic function improved significantly after 6 months of L-T_4 therapy in 10 of 26 randomly selected patients with SHypo (129).

A positive effect on systolic function was observed after replacement therapy in one uncontrolled clinical trial (262) and in four double-blind placebo-controlled trials (109, 133, 134, 249) in which the initially prolonged PEP/LVET ratio significantly decreased after L-T_4 therapy (Table 8). In the study by Cooper *et al.* (109), a significant improvement was seen with L-T_4 only in patients with the highest PEP/LVET ratio (>0.39); changes *vs.* placebo were not statistically significant. Unfortunately, the other three controlled studies did not include a statistical analysis of the results obtained in SHypo patients treated with L-T_4 *vs.* the placebo group (133, 134, 249)

The end-diastolic volume, stroke volume, ejection fraction, and cardiac index increased, and SVR decreased after L-T_4 therapy in a study conducted with MRI (149). Unfortunately, this trial was not placebo-controlled.

Systolic and diastolic function on effort improved after

TABLE 7. Summary of studies examining diastolic function after replacement therapy with L-T_4 in patients with SHypo

First author, year (Ref.)	Response to L-T_4 therapy in SHypo patients				
	No. of patients	TSH (mIU/liter)	TSH after therapy (mIU/liter)	Cardiac findings	Cardiac methods
Biondi, 1999 (129)	10	9.2 ± 4.2	1.7 ± 1	↓ A, ↑ E/A, ↓ IRT	Doppler echo
Monzani, 2001 (133)[a]	10	5.4 ± 2.4	1.17 ± 0.6	↓ A, ↑ E/A, ↓ IRT	Doppler echo
Brenta, 2003 (130)	10	11. ± 4.2	1.9 ± 1.1	↓ TFR	Radionuclide ventriculography
Yazici, 2004 (134)[a]	23	8.4 ± 1.9	2.4 ± 1.3	↑ E/A, ↓ IRT	Doppler echo

TSH values represent mean ± SD. IRT, Isovolumic relaxation time; TPFR, time-to-peak filling rate; E/A, early-to-late transmitral peak flow velocity ratio.

P values for SHypo pretreatment *vs.* posttreatment: IRT, Biondi and Monzani, $P < 0.05$; Yazici, $P < 0.0001$. E/A, Biondi, $P < 0.001$; Monzani, $P < 0.05$; Yazici, $P < 0.0001$. A, Biondi, $P < 0.01$; Monzani, $P < 0.05$. TPFR, Brenta, $P < 0.001$.

[a] Double-blind placebo-controlled.

TABLE 8. Left ventricular systolic function in patients with SHypo before and after replacement therapy

First author, year (Ref.)	No. of patients	Age (yr)	TSH (mIU/liter)	Cardiac findings	Cardiac methods	TSH after therapy (mIU/liter)	Study design
Ridgway, 1981 (262)	20	44 ± 16	28 ± 29	↓ PEP/ET	Weissler's method	1.9 ± 1.4	Uncontrolled study
Cooper, 1984 (109)[a,b]	33	32–71	3.6–39.4	↔ PEP/ET[a]	Weissler's method	2.6 ± 0.5	Randomized double-blind placebo-controlled (1 yr)
Nystrom, 1988 (249)[a]	17	51–73	7.7 ± 3.7	↓ PEP/ET	Weissler's method	1.9 ± 1.8	Double-blind placebo crossover design (2 × 6 months)
Monzani, 2001 (133)[a]	10	32 ± 12	5.4 ± 2.4	↓ PEP/ET	Doppler echo	1.17 ± 0.6	Randomized double-blind placebo-controlled (1 yr)
Yazici, 2004 (134)[a]	23	40 ± 7.9	8.4 ± 1.9	↓ PEP/ET	Doppler echo	2.41 ± 1.3	Randomized double-blind placebo-controlled (1 yr)

Data are expressed as mean ± SD. ET, Ejection time; PEP, preejection period.
P values for SHypo *vs.* control subjects: PEP/ET, Ridgway, $P < 0.001$; Nystrom, $P < 0.01$; Monzani and Yazici, $P < 0.05$.
[a] Double-blind placebo controlled.
[b] ↓ PEP/ET in five patients with highest values (PEP/ET > 0.39).

L-T_4 replacement therapy in patients with SHypo in five studies performed with radionuclide ventriculography, Doppler echocardiography, and cardiopulmonary exercise testing (130, 147, 263–265) (Table 9). However, two studies were not placebo-controlled (130, 147), and three studies (263–265) did not compare pre- and posttreatment values of cardiac performance during exercise in subclinically hypothyroid patients *vs.* the control group. Responses to treatment in all these studies consisted of improvement or correction of the abnormalities of contractile function of the left ventricle with exercise and normalization of diastolic function with exercise.

The impaired muscle energy metabolism could contribute to the reduced exercise tolerance in SHypo. The energy and metabolic response to physical exercise in patients with SHypo was examined at baseline and after 6 months of replacement therapy with L-T_4 in a double-blind randomized placebo-controlled study (251). The pattern of substrate utilization was altered in SHypo patients. However, while improving neuromuscular symptoms, L-T_4 replacement did not cause significant changes in the energy or substrate response to exercise and did not correct this alteration after 1 yr of stable euthyroidism. It remains to be established whether these effects on muscle metabolism are irreversible or whether more time is needed for normalization.

In an uncontrolled study, evaluation with tissue Doppler imaging showed that precontraction times and precontraction-contraction ratios decreased, albeit not significantly, after replacement therapy with T_4 in 22 subclinical hypothyroid patients (TSH 13.3 ± 9.1 mIU/liter). Septal lateral annulus and lateral myocardial relaxation times were significantly decreased after L-T_4 (266).

In summary, all these studies, performed with correct methods to evaluate cardiac function, support the hypothesis that L-T_4 replacement therapy can normalize the hemodynamic alterations induced by SHypo. However, only four studies were double-blind placebo-controlled trials (109, 133, 134, 249).

TABLE 9. Summary of studies examining systolic and diastolic function during exercise after replacement therapy with L-T_4 in patients with SHypo

First author, year (Ref.)	n	TSH (mIU/liter)	Exercise
Bell, 1985 (263)[a,b]	18	17.9 ± 10	↑ SF
Forfar, 1985 (264)[a,b]	10	18.2 ± 9	↑ SF
Arem, 1996 (265)[a,c]	8	14.8 ± 9.5	↑ SF
Kahaly, 2000 (147)[a,d]	20	11.2 (6.3–19.5)	↑ SF
Brenta, 2003 (130)[a,b]	10	110 ± 1.4	↑ DF

TSH values are mean ± SD. SF, Systolic function; DF, diastolic function.
[a] Clinical trial uncontrolled.
[b] Radionuclide ventriculography.
[c] Echocardiography during exercise.
[d] Cardiopulmonary exercise test.

4. Effects of replacement therapy on the vascular system. In uncontrolled clinical trials, appropriate replacement therapy with L-T_4 induced a significant decrease in SVR (149, 157), mean arterial pressure (157), and central arterial stiffness (162) in normotensive subclinically hypothyroid patients. After L-T_4 therapy, there was a significant decrease of the augmentation gradient, augmentation index, corrected augmentation index, and the diastolic brachial and aortic blood pressure (162). However, SVR was unchanged after replacement therapy in two double-blind placebo studies in which SVR was not increased at baseline evaluation (133, 134). After 6 months of stable euthyroidism, endothelial function improved in patients with SHypo in an uncontrolled clinical trial (166). Indeed, there was a significant improvement in acetylcholine-induced vasodilatation and restoration of the inhibitory effect of L-NMMA, indicating that L-T_4 treatment improves endothelium-dependent vasodilatation by restoring nitric oxide availability (166). These results were recently confirmed in a randomized double-blind crossover study of L-T_4 *vs.* placebo (261). Brachial artery flow-mediated dilatation improved significantly after replacement therapy; this effect was independent of other cardiovascular risk factors (261). Finally, Monzani *et al.*, in a double-blind placebo-controlled study of individuals less than age 55, reported that replacement therapy with L-T_4 significantly decreased CIMT. The reduction was directly related to the decrease of both TC and TSH (168).

On the basis of the data available, treatment of SHypo could, in theory, improve the well-being of the vascular system by decreasing SVR, endothelial function, and carotid intimal thickness, and might thereby prevent or reverse atherosclerosis and coronary artery disease. However, only a

few of these studies were randomized placebo-controlled trials, and the results were not concordant (133, 134, 168, 261).

5. Effects of replacement therapy on lipid profile and cardiovascular risk factors. It remains to be established whether or not replacement therapy with L-T_4 lowers serum lipid levels in patients with SHypo. Two meta-analyses have been carried out regarding the effects of L-T_4 therapy on serum cholesterol levels in patients with mild thyroid failure (267, 268). In the first meta-analysis of 13 studies from 1976 to 1995, thyroid hormone replacement therapy decreased TC in patients with SHypo by 0.4 mmol/liter (15 mg/dl) independently of the initial plasma level; however, plasma levels remained elevated in most patients (267). In the other meta-analysis performed in 2000 on 247 patients from 13 selected studies, serum TC was reduced by about 0.2 mmol/liter (8 mg/dl or 5%) and serum LDL-C by about 0.3 mmol/liter (10 mg/dl) after L-T_4 treatment, whereas triglyceride and HDL-C levels did not change (268). The decrease in serum TC concentration was about 0.04 mmol/liter greater (1.6 mg/dl) for each 0.23 mmol/liter (10 mg/dl) increase in the baseline concentration. When the studies were divided according to a mean baseline serum TC cutoff of 6.2 mmol/liter (240 mg/dl), L-T_4 reduced serum TC by 0.4 mmol/liter (16 mg/dl) in cases above the cutoff value, and by 0.02 mmol/liter (0.8 mg/dl) in cases equal to or less than the cutoff point (268). Furthermore, greater changes were seen in those patients with SHypo due to inadequately treated overt hypothyroidism compared with patients with only SHypo at the outset.

It must be emphasized that some of the studies included in these two meta-analyses had important limitations. Only a few studies were randomized with placebo controls, namely, three studies in the meta-analysis by Danese *et al.* (268). Moreover, in many studies the results were obtained in a small number of patients, sometimes using poor selection criteria in terms of etiology and persistence of thyroid disease, the TSH value after replacement therapy was completely different in the various studies, and the period of replacement therapy was different. Thus, in the meta-analysis by Danese *et al.* (268) the changes in cholesterol were much greater in those studies that were judged to be of poorer quality.

More recently eight placebo-controlled randomized clinical trials have been carried out to examine the effects of L-T_4 on serum lipids in SHypo (Table 10). In four of these studies, T_4 did not reduce TC (109, 110, 249, 259), whereas a beneficial effect was found in the remaining four studies (168, 189, 260, 261). The first two randomized trials published found only minimal, nonsignificant reductions of TC levels during L-T_4 therapy and provided no data for LDL-C (109, 249). In another placebo-controlled study, LDL-C was reduced by 3.6% (0.13 nmol/liter) after T_4 replacement therapy, which was not significant (259). Kong *et al.* (110) found no clinically relevant benefit of replacement therapy on LDL-C levels in women with SHypo after 6 months of T_4 therapy *vs.* a placebo group.

In a double-blind placebo-controlled study, Meier *et al.* (260) reported a decrease in TC and LDL-C levels in patients with SHypo after T_4 replacement therapy. The LDL-C decrease was more pronounced in patients with TSH levels greater than 12 mIU/liter or elevated LDL-C at baseline. No significant changes were seen in patients with baseline TC and LDL-C values that were below 12 mmol/liter (260 mg/dl) and 4 mmol/liter (154 mg/dl), respectively. When the results were analyzed as a randomized trial, the mean treatment effects for TC and LDL-C at the end of the study were no different from the intervention group (L-T_4) and the placebo group. Pretreatment LDL-C level was 4.0 mmol/liter in the treatment group *vs.* 3.8 mmol/liter in the placebo group, and the posttreatment LDL-C level was the same in both groups (3.7 + 0.2 mmol/liter; $P = 0.11$).

The effect of L-T_4 therapy on TC and LDL-C was evaluated in another double-blind placebo-controlled study of 49 patients with SHypo (189). Both TC and LDL-C concentrations decreased significantly after L-T_4 therapy in direct proportion to the respective baseline values, whereas lipoprotein (a) levels were unchanged (189). Furthermore, the subgroup of patients with lower TSH value had a lesser reduction in lipid concentrations. However, no changes occurred in the placebo group, and the comparison of the mean treatment ef-

TABLE 10. Summary of double-blind placebo-controlled studies examining lipid abnormalities and responses to replacement therapy with L-T_4 in patients with SHypo

First author, year (Ref.)	n	M/F	Age (yr)	TSH (mIU/liter)	Response L-T_4 therapy in SH patients				
					TC	Serum LDL-C	Serum HDL-C	Serum Lp(a)	Duration (months)
Cooper, 1984 (109)	17	0/17	58 ± 9	10.8 ± 8.8	↔				12
Nystrom, 1988 (249)	17	0/17	58 ± 5	7.7 ± 3.7	↔				6
Jaeshke, 1996 (259)	18		>55	12.3	↔	↔	↔		10
Meier, 2000 (260)[a]	31	0/33	57 ± 11	12.8. ± 7.7	↓	↓	↔	↔	12
				>12.0	↓	↓			
				<12.0	↔/↓	↔/↓			
Kong, 2002 (110)	23	0/23	53 ± 3	8.0 ± 1.5	↔	↔	↔		6
Caraccio, 2002 (189)[a]	49	7/42	35 ± 9	5.4 (3.7–15.0)	↓	↓	↔	↔	6
				>6.0	↓	↓			
				<6.0	↔/↓	↔/↓			
Monzani, 2004 (168)[a]	45	8/37	37 ± 11	6.31 (3.65–15.0)	↓	↓	↔	↔	6
Razvi, 2007 (261)	100	19/81	53.8 +12	5.3 (3.7–15.8)	↓	↓	↔		3

Values are mean ± SD. Lp(a), Lipoprotein (a); M, males; F, females.

[a] Studies in which a greater improvement of lipid profile by L-T_4 occurred in subgroups of SHypo patients with a more elevated serum total or LDL cholesterol.

fects between placebo and L-T_4 treated patients did not reach statistical significance in any of the lipid patterns examined (189).

Increased CIMT represents a marker of underlying atherosclerosis (269). The double-blind placebo-controlled study by Monzani *et al.* (168) showed that L-T_4 replacement therapy significantly reduced both TC and LDL-C *vs.* placebo. The CIMT was found to be significantly higher in young (mean age, 37 yr) SHypo patients than in euthyroid controls (168) and correlated with serum lipids (TC, LDL-C, Apo B, and triglycerides). After 6 months of restored euthyroidism, the mean CIMT was reduced by almost 10%, and the absolute mean CIMT reduction was directly related to the absolute decrements of both serum TC and TSH concentrations. No significant change in biochemical parameters or CIMT was observed in the placebo group. Replacement therapy also reduced the mean CIMT in the subgroup of patients with serum TSH levels lower than 10 mIU/liter. The decrease of mean CIMT was significant in both younger and older patients, and the mean CIMT became equivalent to that of euthyroid controls. The improvement of both the atherogenic lipoprotein profile and CIMT suggests that lipid infiltration of the arterial wall might be a mechanism underlying the increase of CIMT in SHypo.

In the most recent randomized controlled study, a double-blind crossover design was used to evaluate the effects of replacement therapy in 100 patients. L-T_4 therapy significantly reduced TC and LDL-C (5.5% decrease in TC and 7.3% decrease of LDL-C, respectively, from baseline values) (261) with a significant inverse relationship between reduction in TC levels and the increase in FT4 levels. It is noteworthy that in the Helsinki Heart Study, a decrease of only 7% in serum LDL-C levels in men was associated with a 15% reduction in the incidence of coronary heart disease (270).

Recently, the effect of L-T_4 replacement on non-HDL-C levels (a measure of TC minus HDL-C) was evaluated in patients with SHypo. The serum concentrations of TC, non-HDL-C, remnant-like particle cholesterol, and Apo B were significantly decreased in SHypo patients, whereas no significant changes in the serum concentrations of LDL-C, HDL-C, triglycerides, Apo A-I, and lipoprotein (a) were observed (271).

In various studies, lipoprotein (a) (168, 185, 188, 189, 260, 271, 272) and plasma-oxidized LDL-C (177) remained substantially unchanged after replacement therapy in patients with SHypo. However, only a few of these studies were controlled with a placebo group (168, 189, 260). Milionis *et al.* (273) reported a beneficial effect of L-T_4 therapy in patients with increased baseline lipoprotein (a) levels and low molecular weight Apo A isoforms, and Tzotzas *et al.* (185) found a significant decrease in lipoprotein (a) in postmenopausal women. Homocysteine levels were unaffected by treatment of SHypo in three double-blind placebo-controlled studies (168, 190, 274). In a recent study, replacement therapy with L-T_4 to normalize TSH did not modify homocysteine levels in the fasting or postmethionine states in 24 patients with mild hypothyroidism (TSH levels between 5 and 10 mIU/liter) (274).

L-T_4 replacement therapy resulted in a significant decrease in plasminogen activator inhibitor-1 and factor VII, and hence had a beneficial effect on coagulation parameters in patients affected by SHypo in an uncontrolled study (212). Moreover, SHypo was associated with minor changes in factor VIII activity and vWF when compared with euthyroid subjects. These effects were reversed by L-T_4 (213). L-T_4 replacement did not affect CRP levels in a double-blind placebo-controlled study in patients with SHypo (190). In a recent study, both the overt and subclinical hypothyroid groups had higher thrombin activatable fibrinolysis inhibitor (TAFI), an inhibitor of fibrinolysis, than the control group ($P < 0.05$). High levels of TAFI antigen were correlated with the degree of thyroid failure. After achieving a euthyroid state with L-T_4 replacement, TAFI antigen levels decreased significantly in patients with overt and subclinical hypothyroidism ($P < 0.05$) (275).

In summary, four double-blind placebo randomized controlled trials found that replacement therapy may have had a beneficial effect on lipid profile (168, 189, 260, 261). Replacement therapy does not appear to affect lipoprotein (a), homocysteine, or CRP. Controlled studies are necessary to evaluate the effect of L-T_4 on coagulation parameters. It is not easy to draw conclusions about the effects of L-T_4 replacement therapy on cardiovascular risk factors associated with SHypo. The studies carried out on this topic have some limitations, and there are differences in terms of cause and duration of SHypo, sex, age of patients evaluated, TSH level at the baseline evaluation and after replacement therapy, and the period of replacement therapy. TSH values were stratified in only a few studies, which makes it difficult to evaluate the effects of L-T_4 in patients with mild SHypo, *i.e.*, serum TSH levels between 4.5 and 10 mIU/liter.

J. Thyroid hormone deficiency before and during pregnancy

1. Epidemiology. Thyroid function was evaluated in blood specimens in two prospective studies of 12,000 women in Maine who were 17 wk pregnant (276, 277). TSH values were above 6.0 mIU/liter in 2.3% of the women and above 12 mIU/liter in 0.3%. Seventy percent of women with abnormal TSH values had TPO antibodies *vs.* 11% of controls. FT4 concentrations were 2 SD below the control mean in 0.3% of the women with the highest TSH concentrations. Similar results were reported in two other studies (278, 279). In a prospective study of 1900 consecutive pregnant women carried out to evaluate the occurrence of undiagnosed SHypo, the overall prevalence of SHypo was 2.3% (278). Moreover, in 40% of women the cause of hypothyroidism was related to TA (278). In a recent study of 25,756 pregnant women, 0.2% were found to have overt hypothyroidism, and 2.3% had SHypo (279). Moreover, 88% of the subclinically hypothyroid women had a serum TSH concentration below 10 mIU/liter. In a review of 14 articles for a total of 14,148 pregnant women, the prevalence of anti-TPO antibodies and/or TgAb in pregnancy was found to be 10.8%, and there was a strong association with hypothyroidism (280). Therefore, it appears that untreated or inadequately treated chronic autoimmune thyroiditis is the most common cause of thyroid hormone deficiency in pregnancy. Other risk factors for SHypo in pregnancy are diabetes mellitus, iodine deficiency, thyroid ablation or surgery, a family or personal history of thyroid

disease, goiter, history of spontaneous abortion, or any symptom suggesting hypothyroidism (280).

There is a complex relationship between TA and female and male infertility (281–285). Although the mechanisms that link thyroid hormone deficiency or TA to fertility remain to be clarified, TA is clearly associated with infertility in women and miscarriage risk irrespective of thyroid function. Despite this observation, treatment with L-T_4 of TA associated with these conditions remains controversial.

2. Maternal and fetal risk. Recent studies suggest that TA may entail an increased risk of recurrent miscarriage (282–284). It is not known whether the risk is related to TA itself or to a subtle thyroid dysfunction characteristic of SHypo. In a meta-analysis of studies carried out on papers published since 1990, TSH levels in antibody-positive but euthyroid women were higher than in antibody-negative women (283).

The adverse effects of overt maternal hypothyroidism include a higher risk of perinatal mortality, increased risk of fetal death, increased frequency of low birth weight, fetal distress, preterm birth, and impaired mental and somatic development (286, 287). The evaluation of adverse pregnancy outcome in seven recent uncontrolled studies showed a frequency of preterm births in 6% of women with SHypo and in 20% of women with overt disease, whereas the frequency of gestational hypertension was 11% in SHypo and 23% in overt hypothyroidism. The frequency of perinatal mortality was 2.9 and 7% in cases of SHypo and overt hypothyroidism, respectively (287). However, in a study that included a control population, only fetal deaths were increased in women with thyroid hormone deficiency; the frequency was 8.1% in women with a TSH of 6–9.9 mIU/liter and 0.9% in women with TSH less than 6 mIU/liter (280). In another controlled study, only an increased risk of gestational hypertension and low birth weight was reported in women with SHypo (288). Glinoer *et al.* (289) reported that the number of preterm deliveries in women with antithyroid antibodies was double that in a control population. This is also the conclusion of a recent paper by Negro *et al.* (290) who observed a markedly decreased miscarriage and premature delivery rate in women with autoimmune thyroid disease and normal serum TSH values who received thyroid hormone therapy.

Abalovich *et al.* (291) studied 114 women with primary hypothyroidism receiving inadequate L-T_4 treatment. The outcome of pregnancy in overtly hypothyroid and SHypo patients was abortion in 60 and 71.4%, premature delivery in 20 and 7.2%, and term delivery in 20 and 21.4%, respectively. When treatment was adequate, 100% of overtly hypothyroid patients and 90.5% of SHypo patients carried pregnancies to term, and there were no abortions in the group. Although these data are consistent with the importance of adequate treatment of overt hypothyroidism and SHypo during pregnancy to maintain normal serum TSH values, it must be acknowledged in the absence of controlled trials that poorly treated hypothyroidism might be a surrogate for poor medical care. In women with treated hypothyroidism, the L-T_4 dose requirement increases early in pregnancy and may rise by 30–50% of prepregnancy values (292, 293).

3. Intellectual outcome in the offspring of pregnant women with SCTD. Maternal FT4 is critical for fetal brain development and maturation. Fetal thyroid ontogeny begins at 10–12 wk gestation and is not complete until delivery, and T_4 is not secreted until 18–20 wk gestation. Before this time, the fetal brain is dependent on circulating maternal T_4. It has yet to be established whether or not SHypo impairs fetal brain development. Thyroid hormone of maternal origin plays a significant role in fetal neurodevelopment up to 20 wk gestation, and experimental results obtained in the rat strongly support the conclusion that thyroid hormone is already required for normal corticogenesis very early in pregnancy (294–296). For example, T_4 crosses the placenta in a sufficient amount to normalize T_3 concentration in the brain of hypothyroid fetal rats (295). Moreover, T_4 is found in human coelomic fluid as early as 4 wk gestation (297) and in cord blood of newborns with athyreosis or thyroid dysgenesis. This demonstrates the importance of the maternal-fetal transfer of T_4 in hypothyroid newborns who are incapable of synthesizing T_4 (298).

The potential adverse effects of maternal hypothyroidism on fetal development before the start of normal thyroid function are well documented. In 1969, Man and Jones (299) reported that children of hypothyroid mothers inadequately treated had lower IQs than those of adequately treated patients and normal controls. They used measurements of serum butanol extractable iodine to distinguish between euthyroidism and hypothyroidism. These findings were confirmed 30 yr later in an unselected population of 25,000 pregnant women in Maine (300). Women were considered to be hypothyroid if their TSH concentration (measured in sera collected at 17 wk gestation) was equal to or above the 97.7th percentile. Sixty-two women with hypothyroidism were retrospectively identified. Of these, 14 were identified and treated before and during pregnancy with a dose of T_4 that remained constant during pregnancy. The children underwent 15 tests that evaluated intelligence, reading, language, attention, school performance, and visual-motor impairment at approximately 8 yr of age. The full-scale IQs did not differ between the children of the 62 hypothyroid women and those of the 124 controls. However, further examination showed that 33% of the children of the 48 untreated mothers had IQs 1 SD below the control mean *vs.* 15% of the control children and only 7% of the children from hypothyroid mothers treated with L-T_4. However, it must be emphasized that in this study the mean TSH in the T_4-treated patients was higher than in the untreated patients. A subsequent study showed that IQ was inversely correlated with maternal TSH (301).

Suboptimal concentrations of maternal T_4, as occurs in the case of iodine deficiency, might also have a deleterious effect on the intellectual development of offspring. Women in areas of borderline iodine insufficiency (60–100 μg/d) have relative hypothyroxinemia, increased serum T_3/T_4 ratios, and high-normal TSH levels as pregnancy progresses (286). Pop *et al.* (302) evaluated mental and psychomotor development in 220 healthy children at 10 months of age. They were born after uncomplicated pregnancies and deliveries, by mothers with serum TSH within the reference range (0.15–2.0 mIU/liter) during early pregnancy and living in the Netherlands, which is an iodine-sufficient country. Children of women

with FT4 levels below the 5th and 10th percentiles at 12 wk gestation and normal serum TSH levels had an increased risk of delayed psychomotor development at 10 months of age compared with children of mothers with higher FT4 values (relative risk 5.8). These mothers were three times as likely to be TPO antibody-positive (25 *vs.* 8%). Subsequently, Pop *et al.* (303) showed that low maternal plasma FT4 concentration during early pregnancy was an important risk factor for impaired infant development. Mental and psychomotor scores were lower in infants in the low-serum FT4 group at both 1 and 2 yr. Neurodevelopment was delayed in infants whose mothers had low serum FT4 concentrations at 10 wk gestation; neurodevelopment delay was especially pronounced in infants whose mothers had persistently low concentrations. The conclusion of this study supports the hypothesis that maternal FT4 values in the low normal range during early pregnancy are associated with impaired child development. This observation has important clinical implications for pregnant women from iodine-deficient areas.

There is still much to learn about the adverse effects of thyroid hormone deficiency in pregnancy. In the study noted above by Casey *et al.* (279), women with SHypo had a 2-fold higher incidence of preterm delivery, a 3-fold increase in placental abruption, and a significant increase in the proportion of neonates admitted to the intensive-care unit *vs.* euthyroid control women. This study suggests the possibility that the intellectual consequences of SHypo in the long-term outcome of offspring may be related to the effects of prematurity rather than to the thyroid hormone abnormality *per se*. Therefore, the consequences of undiagnosed or untreated SHypo on developing brain might be due in part to insufficient maternal transfer of thyroid hormone to the children and in part to the obstetrical consequences of untreated SHypo.

In conclusion, the data available suggest that L-T_4 therapy for pregnant women with SHypo can reduce pregnancy loss and preterm delivery and improve the outcome of offspring. The thyroid status of women with TA should be monitored during pregnancy. L-T_4 therapy is the preferred method for thyroid hormone replacement in pregnant women and in women contemplating pregnancy. Women with overt and SHypo should be treated, and the L-T_4 dose should be increased during pregnancy if necessary.

4. Screening for thyroid insufficiency during pregnancy. The American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists concluded that there is not enough evidence to determine whether screening for SHypo before or during pregnancy in asymptomatic women is warranted or necessary (5, 527). However, other societies recommend the "case finding" of pregnant women if they are at high risk, and of women with a history of thyroid disease, TA or diabetes mellitus, or a family history of thyroid disease (6, 304). Ideally these women should have their thyroid health evaluated before planning pregnancy and again shortly after becoming pregnant (304). However, a recent prospective study on 1560 consecutive pregnant women, evaluated by TSH, FT4, and FT3 during their first prenatal visit, showed that at least one third of pregnant women with thyroid disease can be missed by a high-risk case finding approach (305).

More research is required to establish normal ranges for serum thyroid hormone and TSH levels during each trimester of gestation. Before deciding whether screening is of value, it is important to establish which thyroid tests are optimal and when they should be performed. Other issues that remain to be determined are: the TSH threshold for treatment in mild thyroid deficiency, the role of thyroid hormone deficiency or autoimmunity during gestation, and the effects of replacement therapy in mild thyroid hormone deficiency. A prospective randomized controlled study is currently being conducted by J. H. Lazarus and colleagues (University of Wales College of Medicine) to test the value of screening for thyroid disease and the effect of treatment in women with increased serum TSH.

K. Subclinical hypothyroidism in the elderly

The thyroid gland undergoes several anatomical changes with age. There is a reduction in weight of the gland, in the size of follicles, and in the content of colloid, and increased fibrosis often with marked lymphocytic infiltration. However, these changes do not correlate with thyroid function. The half-life of T_4 increases to 9.3 d in the seventh decade of life (306). Serum T_4 concentration is not affected by this change because its production decreases with age. Although studies of heterogeneous populations suggested that T_3 levels decline with age, studies of selected healthy people indicated that T_3 levels are unaffected by aging (307). TSH may increase or decrease with age in relation to the iodine intake (16, 308); however, the very elderly (octogenarians and beyond), may have a mild TSH decrease (309), suggesting the presence of an "altered set point" of the hypothalamic-pituitary-thyroid axis in some elderly individuals (310).

There is an age-dependent increase in the prevalence of antithyroid antibodies in the ambulatory population. From 40 to 70% of older subjects with elevated TSH concentrations have thyroid autoantibodies, however only a minority of older patients with thyroid autoantibodies have elevated TSH. The increase in thyroid autoantibodies with age seems to be due to the effect of age-associated disease rather than aging *per se* (16, 308, 309). The percentage of people with positive TPO antibodies decreased in subjects older than 80 yr, suggesting either that antithyroid antibodies decline after age 80 or that TPOAb-positive patients die (306).

SHypo is prevalent in the elderly population, especially in women, and may progress to overt disease (16, 24, 40, 65, 75–78, 89). The causes of SHypo in the elderly are similar to the causes of SHypo in young and middle-aged patients, previously described. Autoimmune thyroiditis and treatment of hyperthyroidism are the main causes of thyroid hypofunction in patients older than 55 yr (92). SHypo may remain unrecognized in the elderly especially if the decline in thyroid function is gradual. In some cases, the manifestations of thyroid hormone deficiency in the elderly may be erroneously attributed to the effects of aging (311, 312). Among the drugs that may induce thyroid hormone deficiency, amiodarone, lithium, and interferon-α are frequently administered in the elderly (311). The risks associated with SHypo in the elderly, like those in younger patients,

are hypertension, atherogenic dyslipidemia, atherosclerosis, decreased cardiac function, and muscle dysfunction. The cardiovascular risk may be further increased in older subjects because they are more likely to have an underlying heart disease.

It remains to be established whether or not elderly patients with SHypo should be treated (5, 6). Most professional organizations and an evidence-based guideline advocate starting replacement therapy in elderly patients who have TSH concentrations greater than 10 mIU/liter and in those with antithyroid antibodies (6), and in symptomatic elderly patients with TSH levels between 4.5 and 10 mIU/liter (5). From a cardiovascular viewpoint, it seems reasonable to be concerned about treating SHypo in the elderly for fear of increasing the oxygen demand of the heart. On the other hand, replacement therapy could improve cardiac function thereby reducing SVR, which in turn would reduce the risk of diastolic heart failure and of atherosclerosis. However, there are no data on the effects of replacement therapy on the cardiovascular system in elderly patients.

Evidence suggests that the effect of replacement therapy on health outcome could be more complex in elderly patients than in other age groups (92). In a recent study, SHypo was a risk factor for depression in 323 elderly individuals over 60 yr old (313). In an observational, population-based prospective follow-up study carried out in Leiden, The Netherlands, 559 individuals were followed up from the ages of 85 through 89 yr (92). Thyroid status was assessed at baseline and during follow-up. No patients were treated regardless of thyroid status. At annual visits, investigators evaluated daily life activities and cognitive and affective function. At baseline and during follow-up, there was no association between SHypo or overt hypothyroidism and lessened physical function, depressive symptoms, and cognitive function. At the end of follow-up, no patient with SHypo at baseline had progressed to overt hypothyroidism (92). Both overt hypothyroidism and SHypo were associated with lower mortality, and higher levels of T_4 were associated with increased mortality after adjusting for sex, disability, and health status. In support of these data, low serum FT4 was recently associated with a better 4-yr survival in a population of independently living elderly men (314). There was an inverse relationship between T_3 and physical performance and lean body mass, and between FT4 and mortality, which suggests that a lower activity of the thyroid hormone axis is beneficial during aging and could be an adaptive mechanism to prevent excessive catabolism (314).

Thyroid hormone deficiency may exert protective effects in the elderly, namely a lower metabolic rate, reduced adrenergic tone, and the protective effects of hypothyroidism in case of acute events. Moreover, in theory, very elderly patients (*e.g.*, above 85 yr of age) may be biologically different from moderately old patients (*e.g.*, 60–70 yr). In fact, octogenarians with higher blood pressure values tend to live longer than those with lower values (315). Moreover, several risk factors associated with thyroid hormone deficiency (TC and LDL-C levels) are powerful, independent cardiovascular risk factors in the middle-aged, but not in the very elderly (316).

In conclusion, more information is needed as to the normal reference range for TSH in the elderly. The benefits of treating very elderly subjects with SHypo are uncertain. Moreover, other chronic diseases are often associated with a heterogeneous health status in subjects older than 65 yr. Although large randomized trials are needed, limited evidence suggests that treatment of SHypo should probably be avoided in patients older than 85 yr whose TSH level is between 4.5 and 10 mIU/liter (92). After the identification of elderly patients who would benefit from replacement therapy, treatment should be individualized in those with a serum TSH concentration above 10 mIU/liter. In such cases, L-T_4 therapy can be initiated with the aim of reaching a TSH serum level of 4–6 mIU/liter in individuals older than 70 yr (317). It must be noted that overtreatment with excessive L-T_4 doses can have negative consequences in the elderly (317). Prospective therapeutic trials are necessary to clarify the necessity of replacement therapy in the elderly.

L. Subclinical hypothyroidism in children

Congenital hypothyroidism occurs in approximately one in 3000–3500 babies in the United States. This condition may lead to severe, irreversible mental retardation. Infants with congenital hypothyroidism often appear normal at birth. Therefore, it is recommended that all newborns undergo thyroid tests when they are between 3 and 5 d old. Congenital hypothyroidism is diagnosed in approximately 30% of all newborns with elevated TSH, and the infants are immediately given L-T_4 replacement therapy. However, most newborns with elevated TSH levels (60–70%) have normal or nearly normal TSH and FT4 at recall examination.

A prospective study was carried out in 56 false-positive newborns with elevated serum TSH and normal FT4 at birth and normal or borderline high/normal TSH at recall examination (318). Evaluation of thyroid function at birth, in the neonatal period, and at 2–3 yr of age showed that persistent SHypo in early childhood was very frequent (70%) among false-positive children who had slightly elevated serum TSH concentrations (5–12 mIU/liter) at recall examination. These results suggest that all infants with elevated serum TSH at neonatal screening are at risk of SHypo in early childhood and require follow-up (318).

Hashimoto's thyroiditis is the most common cause of thyroid disease in children and adolescents, and it is often found in patients with type I diabetes and other autoimmune disorders such as celiac disease, polyglandular autoimmune disorders, and juvenile idiopathic arthritis (319, 320). An increase in the prevalence of autoimmune thyroiditis among schoolchildren was reported after iodine prophylaxis in Greece (321). An increased serum TSH concentration was also seen (0.96%) in children with autoimmune thyroiditis (2.92%) in Sardinia, which is an area of moderate iodine deficiency (322). A significant increase of autoimmune thyroid disease was observed in girls older than 11 yr, which suggests that puberty can be a factor in determining the prevalence of TA (322). The clinical course of autoimmune SHypo in children is variable, and spontaneous remission may occur in adolescence (94, 323). Thyroid hormone deficiency is frequent in patients with Down syndrome (324). Patients with Turner's syndrome are also at a higher than average risk of developing autoimmune thyroid disease not

only in adolescence and adult age but also in childhood. SHypo is the most frequent thyroid dysfunction (325). Among hematological conditions, patients with β-thalassemia major and patients who received bone marrow transplantation during childhood or adolescence were found to have an increased risk of SHypo in two studies without a control population (326, 327).

The clinical features of SHypo in children are goiter, menstrual disorders, and possibly short stature (319). SHypo was associated with an increased risk of symptomatic hypoglycemia in children and adolescents with type 1 diabetes mellitus (328). Interestingly, a recent study showed a better performance and cognitive function in adolescents with SHypo than in the euthyroid group, even after adjustment for sex, age, and family income level (329). SHypo does not increase the risk of myocardial structural or functional abnormalities in children with Down syndrome and SHypo (330). Among parameters of cardiovascular risk, plasma homocysteine concentrations were not increased in adolescents with SHypo (331). HDL-C levels were significantly lower in 46 children with TSH greater than 4.65 mIU/liter (332). These findings could indicate that an atherogenic lipid profile can occur in adolescents.

Very few studies have examined the effects of L-T_4 replacement therapy in young people with SHypo. In an uncontrolled study, SHypo was detected in 39 (1.9%) of 2067 young patients with short stature in a study performed in 1989, in which the disease was identified by the TRH test (333). After 1 yr of L-T_4 replacement therapy, growth velocity and the growth velocity SD score improved in prepubertal and pubertal patients; the improvement was more significant in the pubertal group. A longitudinal study on long-term L-T_4 therapy in 13 adolescent girls with SHypo caused by chronic lymphocytic thyroiditis did not adversely affect bone mineral density (BMD) or bone turnover, which indicates that attainment of peak bone mass is not impaired by L-T_4 (334). A double-blind crossover placebo-controlled trial involving children and adults with Down syndrome and SHypo failed to document any cognitive, social, or physical changes attributable to 8–14 wk of T_4 treatment (335). However, treatment duration was probably too short to identify effects of replacement therapy.

In conclusion, controlled studies are needed to assess the effect of replacement therapy in children with SHypo. For those not taking thyroid hormone, thyroid function should be periodically evaluated because SHypo may regress or may progress. Obviously, replacement therapy with L-T_4 is not necessary in children who spontaneously normalize serum TSH.

M. Screening for hypothyroidism

SHypo is easily diagnosed with a TSH test. The ATA recommends that adults be screened for thyroid dysfunction at the age of 35 yr and every 5 yr thereafter (336). More frequent TSH tests are suggested for individuals with signs and symptoms potentially attributable to thyroid dysfunction and those with risk factors (336). Indeed, screening for mild thyroid failure was considered cost-effective when compared with other widely used preventive medical interventions (breast cancer and hypertension), particularly in elderly women (337). Nevertheless, neither the American College of Physicians nor the Institute of Medicine of the National Academy of Sciences recommends general population screening for mild thyroid failure on the basis that the potential benefits of early detection and treatment might be outweighed by the associated cost of therapy and follow-up testing (338, 339). Similar conclusions were drawn by a panel of 13 experts (7), The Royal College of Physicians (340), and the U.S. Preventive Service Task Force (341). In contrast, a non-evidence-based consensus statement from the American Association of Clinical Endocrinologists, The Endocrine Society, and the ATA recommended routine screening for SCTD in the general population (5).

Screening for mild thyroid failure is recommended by some scientific/medical societies in specific high-risk subjects such as the elderly (5, 6, 338, 342) and pregnant women (5, 343). The American Academy of Pediatrics recommends that children with Down syndrome have a thyroid function test at 4–6 and 12 months of age and annually thereafter (344). Screening is defined as testing for a disease in the absence of symptoms, with the goal of improving not only quality of life but also the outcome. Currently, there are not sufficiently robust data about the potential beneficial effect of replacement therapy on the outcome of SHypo. On the other hand, SHypo may progress to overt hypothyroidism, and it has been argued (336) that treatment of SHypo diagnosed through screening would prevent the subsequent morbidity from overt hypothyroidism in such cases. Whether the costs of screening are outweighed by the potential benefits remains to be seen, although one analysis suggested that it was cost-effective (337).

N. Treatment of subclinical hypothyroidism

Whether to treat SHypo remains a dilemma (345, 346). Most clinicians treat SHypo patients who have a serum TSH concentration above 10 mIU/liter, whereas opinions differ about the management of mild disease in which TSH ranges between 4.5 and 10 mIU/liter, especially in elderly asymptomatic patients. Some endocrinologists support the idea that treatment is indicated in patients with SHypo, even those with a mild TSH increase, in the presence of risk factors (1, 8, 347), whereas others believe that treatment is seldom necessary (6, 9, 348).

A panel of 13 experts (eight had expertise in thyroid disease, and eight had expertise in cardiology, epidemiology, biostatistics, evidence-based medicine, health service research, general internal medicine, and clinical nutrition) was convened to propose evidence-based guidelines for the diagnosis, treatment, and screening of SCTD (6). The panel concluded that there was not sufficient evidence to recommend routine treatment for patients with TSH between 4.5 and 10 mIU/liter and suggested that patients be monitored at 6- to 12-month intervals. Although dyslipidemia was considered proven only in patients with TSH above 10 mIU/liter, treatment was recommended in patients with TSH above 10 mIU/liter because of their high rate of progression to overt hypothyroidism (6). The three societies that sponsored the consensus panel (the American Association of Clin-

ical Endocrinologist, The Endocrine Society, and the ATA) considered the recommendations against treatment and screening inappropriate because they were based on a lack of evidence for benefit rather than evidence for a lack of benefit (5). The three societies recommended routine treatment of patients with SHypo who had serum TSH levels of 4.5–10 mIU/liter. Moreover, measurement of anti-TPO antibodies was deemed useful in predicting the risk of developing overt hypothyroidism or associated autoimmune disease.

The factors that influence a clinician's decision to treat SHypo were evaluated in 539 patients whose serum TSH was between 5.1 and 10.0 mIU/liter (349) T_4 therapy was prescribed in 39% of patients with TSH levels between 5.1 and 10 mIU/liter. Among these, patients with thyroid-positive autoantibodies, those with higher TSH values, and those with lower FT4 were more likely to receive T_4 replacement therapy. Younger patients (31–50 yr) were more likely to be treated than older patients (61–80 yr) (349).

It seems reasonable to treat symptomatic patients, those with cardiovascular risk factors, pregnant women, patients with goiter and a positive thyroid antibody test, and subjects with ovulatory dysfunction and infertility because there is evidence of the potential reversibility of these dysfunctions associated with mild thyroid failure (1, 123, 346, 347) (Fig. 3). Treatment of persistent mild SHypo with appropriate doses of L-T_4 to normalize serum TSH may be of benefit from a cardiovascular perspective, although data showing this to be clinically relevant are lacking. Replacement therapy with L-T_4 may reverse the systolic and diastolic dysfunction, arterial hypertension, increased central arterial stiffness, endothelial dysfunction, and other cardiovascular risk factors associated with this condition (123, 347). However, although cardiovascular risk factors have been associated with SHypo in some studies, epidemiological studies in which cardiovascular morbidity and mortality have been evaluated had yielded conflicting results, and there are no data showing that therapy with T_4 improves outcomes such as cardiac morbidity or mortality. More randomized controlled trials and longitudinal studies are necessary to evaluate whether replacement therapy with T_4 reduces the risk of CHD in subjects with SHypo. In the meantime, it could be useful to identify and consider L-T_4 replacement in higher-risk patients with SHypo with the aim of reducing cardiovascular risk. In high-risk individuals, it is reasonable to ascertain whether hyperlipidemia, diastolic hypertension, diastolic dysfunction, or other possible associated cardiovascular risk factors may be improved with replacement therapy. Current data suggest that middle-aged individuals may benefit more from treatment than the elderly (38, 92, 230). T_4 therapy is able to lower the chance of miscarriage and premature delivery in pregnant women with SHypo (350).

L-T_4 is the drug of choice for the treatment of SHypo. It is inexpensive and it stabilizes thyroid hormone levels. There is no reason to use T_3, and there is no evidence of benefit from combined T_3 and T_4 therapy (351, 352). Small doses, *i.e.*, 25–75 μg/d, are often adequate to normalize serum TSH levels in SHypo. The L-T_4 replacement dose should be carefully adjusted to avoid iatrogenic hyperthyroidism. The goal of L-T_4 therapy in patients with persistent mild thyroid failure could

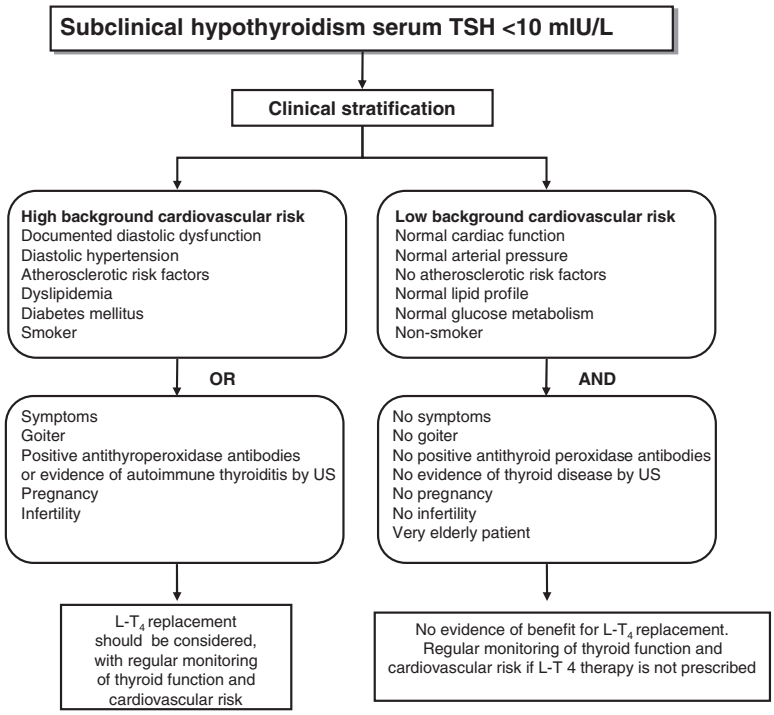

FIG. 3. Algorithm for the diagnosis and treatment of SHypo. This algorithm is based on data showing an increased all-cause mortality (194), increased risk of atherosclerosis (193), coronary events (38, 193, 194, 196), and CHF (231), infertility and maternal and fetal risk (281–291, 299–301), and progression to overt hypothyroidism in autoimmune thyroiditis (24, 90, 93) and on double-blind placebo-controlled studies showing an improvement after replacement therapy of goiter (252–254), symptoms (109, 249, 259, 260), cardiac function (109, 133, 134, 249), vascular system (168, 261), and lipid profile (168, 189, 260, 261).

be a TSH level between 1 and 2–3 mIU/liter in young and middle-aged patients. Once optimal therapy has been achieved, periodic evaluations of serum TSH levels are required to ensure that replacement therapy is not under- or overprescribed. A TSH test should be performed every 6 to 12 months. It is often necessary to increase the L-T_4 dosage progressively with time because of further impairment of the thyroid gland and progression to overt hypothyroidism. In case of suppressed TSH, the L-T_4 dose should be lowered. If a low TSH persists, or if very low doses of L-T_4 normalize thyroid function, thyroid tests should be carried out after L-T_4 withdrawal to evaluate whether SHypo is permanent.

The risks associated with L-T_4 replacement therapy in subclinical hypothyroid patients are: 1) risk of starting L-T_4 therapy in subclinical hypothyroid patients who have clinically established coronary disease; 2) risk of treating elderly subclinical hypothyroid patients especially in the presence of underlying heart disease; and 3) risk of iatrogenic SHyper due to overzealous hormonal dosing with insufficient biochemical monitoring.

In epidemiological studies, the risk of CHD was increased in young and middle-aged patients (38, 193, 194, 196) but not in elderly patients (229–231) with SHypo (353) (Fig. 4). Indeed, SHypo appeared to exert a protective cardiovascular effect in patients older than 85 yr (92). On this basis, treatment of SHypo is not indicated in very elderly patients if serum TSH is lower than 10 mIU/liter (317), especially in the presence of documented cardiac disease. Moreover, when contemplating replacement therapy in very elderly patients with TSH above 10 mIU/liter, it should be started at very low doses (12.5–25 μg/d) and gradually increased because of possible underlying heart disease. The dose can be gradually increased every 4–8 wk in relation to the serum TSH and cardiac symptoms. If angina develops or worsens and is resistant to medical therapy, L-T_4 therapy should be discontinued, and surgery or angioplasty for coronary artery disease should be considered when the patient is still hypothyroid. Low doses of L-T_4 are often adequate in elderly patients because of decreased T_4 metabolism. A reasonable target TSH level should be 3–4 mIU/liter in individuals between 60 and 75 yr old and 4–6 mIU/liter in individuals older than that.

Approximately 20% of L-T_4-treated patients have decreased serum TSH, which usually indicates overtreatment. Physician education can improve this situation, and inadvertent overtreatment should not be used as an argument against L-T_4 replacement therapy in subjects with SHypo. All drugs have adverse effects if given without appropriate safeguards, but if properly monitored to maintain a normal serum TSH concentration, L-T_4 therapy is certainly safe. Tertiary prevention, *i.e.*, care of an existing disease to detect progression and treatment monitoring to assess compliance and to prevent complications, has been advocated for SCTD. Tertiary prevention seems to be underused in the United States, considering that only 60% of patients receiving thyroid hormone had normal thyroid function (354).

Treatment of patients with SHypo during pregnancy is a special issue (355). Serum TSH levels should preferably be checked before pregnancy, and in our opinion L-T_4 therapy should be started if serum TSH is greater than 2.5–3 mIU/liter in the presence of thyroid autoantibodies (290). The mean replacement dose of L-T_4 during pregnancy is about 2.0 μg/kg·d. The magnitude of L-T_4 dosage increment depends on the etiology of hypothyroidism and increases as the degree of underlying thyroid deficiency increases, with an average of 30–50% (355). In patients with mild SHypo, the dose may not increase at all. Women of childbearing age should have an average iodine intake of 150 μg/d. During pregnancy and breast-feeding, women should increase their daily iodine intake to 250 μg/d (355). TSH should be monitored every 6–8 wk during pregnancy and sooner (after 4–6 wk) if L-T_4 dosage adjustment was required because of increased serum TSH levels. Iron and calcium supplementation should not be given together with L-T_4 in order not to affect L-T_4 absorption.

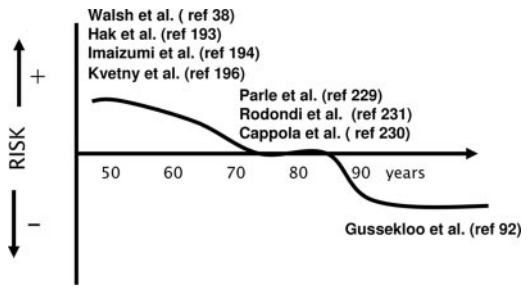

FIG. 4. Hypothetical relationship between age and effect of SHypo on cardiovascular disease. Published data suggest that the possible effects are age related.

VI. Subclinical Hyperthyroidism

SHyper is defined by low or undetectable serum TSH and normal FT4 and FT3 concentrations (3, 4). This entity emerged as a distinct entity as the sensitivity of TSH assays increased. SHyper was first identified from a reduced nocturnal TSH surge or a blunted TSH response to TRH (356). With the second-generation immunometric TSH assays, it became possible to discriminate between patients with subnormal TSH values and normal subjects (357). Third-generation assays, which have a functional sensitivity of 0.01–0.02 mIU/liter, discriminate complete suppression from incomplete suppression of TSH in patients with SHyper and other clinical conditions (358, 359). Although thyroid hormones are defined as being within normal range in patients with SHyper, they are often at the upper limit of the reference range, and thus sufficiently increased to suppress TSH and potentially produce abnormal tissue effects.

A. Subclinical hyperthyroidism and minimally suppressed TSH

A recent panel of experts classified patients with SHyper into two categories: patients with low but detectable serum TSH (0.1–0.4 mIU/liter), and patients in whom serum TSH was undetectable (<0.1 mIU/liter) (6). We shall examine the causes, epidemiology, likelihood of progression to overt hyperthyroidism, the clinical implications, and treatment suggestions using these two definitions of SHyper.

B. Etiology of subclinical hyperthyroidism

The most common cause of SHyper is exogenous SHyper due to unintentional excessive replacement therapy in hypothyroid patients or to intentional TSH suppressive therapy for benign or malignant thyroid disease (4, 360–365) (Table 11). Endogenous SHyper is commonly associated with autonomous thyroid function as occurs in Graves' disease, multinodular goiter, and solitary autonomously functioning thyroid nodules (AFTN) (3, 4, 360, 361, 364, 365). In Graves' disease, SHyper may resolve spontaneously without treatment. Alternatively, it may be transitory during treatment with antithyroid drugs or after radioiodine therapy (because of delayed recovery of the suppressed pituitary thyrotrophic cells) (364), or it may be persistent because of the continued thyroidal autonomy. Long-standing SHyper with a progressive increase in thyroid hormone levels, sometimes preceding the onset of overt hyperthyroidism, is frequent in patients with multinodular goiter and autonomously functioning thyroid adenoma (3, 4).

It remains to be established whether or not exogenous and endogenous SHyper are similar conditions that exert the same effects. Serum FT4 concentrations are at the upper limits of normal range or frankly elevated in many patients undergoing L-T_4 suppressive therapy. In these patients, serum T_3 and FT3 are usually in the middle of their reference ranges, and the T_4/T_3 ratio is greater than in patients with endogenous SHyper (366, 367). Indeed, in the natural history of thyroid autonomy, serum T_3 levels start to rise before T_4 levels rise. Moreover, exogenous SHyper is characterized by constant TSH suppression during intentional suppressive treatment with L-T_4 and may differ from endogenous SHyper in terms of the rate and the duration of the rise in thyroid hormone level.

C. Differential diagnosis in subclinical hyperthyroidism

It is important to differentiate SHyper from other causes of transient TSH suppression (Table 12). Transient TSH suppression usually occurs during subacute, silent, or postpartum thyroiditis. The differential diagnosis of a low serum TSH level includes diseases other than SHyper, namely nonthyroidal illness, psychiatric illness, drug administration (high-dose steroids, dopamine, or dobutamine) and pituitary dysfunction (3, 4, 360, 368). Thyroid hormone levels are usually low in nonthyroidal illness. However, although low, serum TSH can usually be detected with a third-generation TSH assay. Pituitary dysfunction is suggested by a persistently decreased serum TSH concentration associated with low or low normal serum thyroid hormone levels. In addition, TSH concentration may be below the normal range in some elderly patients as a result of an age-related decrease in thyroid hormone clearance (369) or an altered set point of the hypothalamic-pituitary-thyroid axis.

TABLE 11. Causes of persistent SHyper

Endogenous causes
Graves' disease
Autonomously functioning thyroid adenoma
Multinodular goiter
Exogenous causes
Excessive thyroid hormone replacement therapy
Intentional thyroid hormone suppressive therapy

TABLE 12. Other causes of low TSH that are not related to thyroid overactivity

Nonthyroidal illness
Psychiatric illness
Administration of drugs (dopamine, glucocorticoids)
Pituitary or hypothalamic insufficiency
Decreased age-related thyroid hormone clearance or pituitary "set point"

Candidates for treatment can be identified by persistent SHyper documented by repeatedly subnormal or undetectable serum TSH levels and normal free thyroid hormone levels, together with a detailed medical history and detailed clinical evaluation. For example, in the presence of suppressed TSH, it is important to exclude the recent administration of an iodinated contrast agent or excessive iodine exposure. If necessary, 24-h thyroidal radioactive iodine uptake and scan will differentiate between the increased uptake in patients with Graves' disease, the presence of warm or hot nodule(s) in multinodular goiter and autonomously functioning thyroid adenoma, and the absence of uptake in patients in the hyperthyroid phase of thyroiditis and in patients who are taking exogenous thyroid hormone or iodine-containing preparations. Lastly, SHyper may be present in women affected by hyperemesis gravidarum or by trophoblastic disease with high serum human chorionic gonadotropin concentrations (4, 360).

D. Prevalence of subclinical hyperthyroidism

The prevalence of exogenous and endogenous SHyper in the general population is between 0.7 and 12.4% (368). SHyper is common during L-T_4 therapy, being present in about 10–30% of patients (16, 40, 370). Endogenous SHyper is more prevalent in women than in men and in the elderly. Graves' disease is prevalent in areas of high iodine intake, whereas toxic nodular goiter is more prevalent in areas where iodine intake is low (371).

In the Whickham survey, which was carried out between 1972 and 1974, before ultrasensitive TSH assays became available, the prevalence of SHyper defined as a serum TSH concentration less than 0.5 mIU/liter was 10% in women but 0% in men (75). The prevalence of SHyper (TSH $<$ 0.1 mIU/liter) was 2.5% in 968 U.S. subjects over the age of 55 yr, about two thirds of whom were taking thyroid hormone preparations (372). In a study carried out in England, the prevalence of SHyper (TSH $<$ 0.5 mIU/liter) was 6% (373). In the Colorado cross-sectional study of 25,862 subjects, SHyper (TSH $<$ 0.3 mIU/liter) was found in 0.9% of 24,337 individuals, but was present in 20.7% of the 1,525 individuals who were taking thyroid hormone preparations (40).

In the NHANES III study, the prevalence of SHyper (TSH $<$ 0.1 mIU/liter) was 0.7% in people over 12 yr of age (16). However, with a TSH cutoff of 0.4 mIU/liter, the prevalence of SHyper reached 3.2%. The percentage of people with TSH less than 0.4 was significantly higher in females than males in the three population groupings ($P < 0.05$). The

percentage with TSH no greater than 0.4 mIU/liter was significantly higher in blacks than in whites ($P < 0.01$) .

In another U.S. study of 3242 pre- and early perimenopausal women, the prevalence of SHyper (TSH < 0.5 mIU/liter) was 3.2% (374). With a serum TSH cutoff below 0.1 mIU/liter, the prevalence of SHyper was 3.9% in the Framingham Heart Study of 2575 ambulatory persons older than 60 yr; also in this study about half of them were taking thyroid hormones (375). In the recent Cardiovascular Health Study of 3233 U.S. community-dwelling individuals aged 65 yr or older, the prevalence of SHyper (TSH 0.10–0.44 mIU/liter) was 1.5% (230). In Sweden, 1.8% of 886 subjects 85 yr of age or older had SHyper (376).

The prevalence of thyroid autonomy is inversely correlated with the population's iodine intake (377). In a cross-sectional survey carried out in Germany, which is an iodine-deficient area, the prevalence of SHyper, defined as serum TSH less than 0.3 mIU/liter, was 11.3% in the 20- to 79-yr-old group (378). However, with a TSH cutoff below 0.1 mIU/liter, the SHyper prevalence was 1.8%. The prevalence of the disease was similar among women and men, but it increased in the elderly (378). The prevalence of endogenous SHyper due to AFTN and multinodular goiter has been evaluated in two iodine-deficient areas of Italy (23, 379). The prevalence of AFTN was 4.4% and the prevalence of toxic nodules was 1.3% in the study from northeastern Sicily performed in 1983 on 31,373 subjects who were referred to a center of thyroid disease between 1965 and 1980 (379). Methods for the measurement of thyroid hormones in this study were protein-bound iodine until 1970 and then RIA (379). The prevalence of functional autonomy was 6.4% in the Pescopagano survey in which SHyper was defined by TSH less than 0.4 mIU/liter. It progressively increased with age, reaching 15.4% in subjects above the age of 75 yr (23).

In conclusion, the prevalence of endogenous SHyper depends on the cause of the disease, sex, age, iodine intake, the sensitivity of the methods used to measure serum TSH concentrations, and the investigator's definition of the lower limit of the normal range. This variability can explain the differences in the prevalence of endogenous SHyper reported in various studies.

E. Natural history of subclinical hyperthyroidism

The frequency with which SHyper progresses to clinically overt disease is uncertain and depends on the initial serum TSH concentration and on the cause of endogenous SHyper. Some studies of subjects with SHyper monitored for 1–4 yr suggested that SHyper may develop into overt disease at a rate of 1–5% per year (76, 369, 375, 376, 380). In the study by Sawin *et al.* (369), of 33 patients older than 60 yr with SHyper (TSH less than 0.1 mIU/liter) there was a 4.1% rate of progression over 4 yr. Tenerz *et al.* (381) reported that 33 elderly patients with SHyper (TSH < 0.1 mIU/liter) had a higher prevalence of multinodular goiter than matched controls (68 *vs.* 29%). These subjects were more likely to develop overt thyrotoxicosis (30% hyperthyroid, 23% remained with suppressed TSH, and 10% normalized TSH) during 2 yr of follow-up (381). In a 12-month follow-up study of 66 patients older than 60 yr with SHyper, serum TSH evaluated with a sensitive assay reverted to normal in 38 of 50 patients with subnormal but detectable TSH and remained subnormal in 14 of 16 patients with undetectable TSH; only one patient developed hyperthyroidism (76). This study suggests that progression of subclinical to overt hyperthyroidism is less frequent in patients with low serum TSH (1.2% per year) than in patients with undetectable TSH (76). In a study of 15 patients older than 60 yr with SHyper and serum TSH concentration less than 0.1 mIU/liter monitored for 4–12 months, TSH reverted to normal in seven and remained suppressed in eight, and there was progression to overt hyperthyroidism in two patients (382). Similarly, in 33 patients older than 60 yr with a serum TSH less than 0.1 mIU/liter monitored for 4 yr, TSH reverted to normal in 24 patients and remained low (0.1–0.4 mIU/liter) in nine, and there was progression to overt hyperthyroidism in two (369). Moreover, in the study by Parle *et al.* (229), during 10 yr of follow-up of 70 patients older than 60 yr, three (4.3%) developed overt hyperthyroidism.

Few data are available about the natural history of autonomously functioning thyroid adenoma. In a retrospective analysis of AFTN by Hamburger (383), 14 of 159 untreated patients with SHyper became overtly thyrotoxic over a 6-yr follow-up period. Most patients who developed overt hyperthyroidism had nodules more than 3 cm in diameter. Woeber (384) retrospectively examined the natural history of 16 ambulatory patients with SHyper monitored for a cumulative follow-up of 11–36 months. Serum TSH reverted to normal in five of the seven patients with subclinical Graves' disease and remained subnormal in all nine patients with multinodular goiter. Only one of the seven patients with subclinical Graves' disease developed overt hyperthyroidism, whereas none of the nine patients with multinodular goiter progressed to overt disease. This study suggests that the natural history of SHyper depends on the cause of the disease: it is often reversible and occasionally progressive in subclinical Graves' disease, whereas it may be more likely to persist unchanged in cases of multinodular goiter. Moreover, in the study by Brownlie and Legge (385), of 93 euthyroid patients with a history of hyperthyroidism, persistent SHyper with subnormal TSH values occurred in 24% of patients previously treated with antithyroid drugs and was predictive of relapse to overt hyperthyroidism. Finally, it has been reported that SHyper is frequent in elderly patients with multinodular goiter in areas of iodine deficiency, and that overt hyperthyroidism can develop after an acute increase in the supply of iodine (386, 387).

The results of all these studies suggest that serum TSH concentration should be regularly monitored in patients with endogenous SHyper to evaluate whether the disease is persistent or progressive. This is particularly true before deciding whether to treat young and middle-aged patients. In elderly patients, atrial fibrillation (AF) could be the first manifestation of SHyper (381); consequently, treating these patients earlier rather than later should be seriously considered.

F. Symptoms and quality of life in subclinical hyperthyroidism

As in patients with SHypo, the decision to treat patients with SHyper is often based on the assessment of the clinical symptoms and signs, which can be mild. As in overt disease, this evaluation can be performed by assessing specific symptoms and signs, or more generally by testing the quality of life. It is particularly important to consider the age of patients with SHyper, because the presence of symptoms and signs of hyperthyroidism are often masked in the elderly even in patients with severe overt disease (388, 389). Furthermore, the clinical consequences of SHyper are potentially far more significant in the elderly, compared with younger individuals.

1. Symptoms and quality of life in exogenous SHyper. Three studies assessed the presence of symptoms and signs of hyperthyroidism in patients with SHyper compared with normal subjects (390–392). Evaluated with a symptom rating score (SRS), patients with exogenous SHyper were found to have more specific symptoms and signs of overt hyperthyroidism, with a higher prevalence of palpitations, tremor, heat intolerance, sweating, nervousness, anxiety, reduced feeling of well-being compared with normal subjects (390–392). Seventeen athyreotic patients, aged 45 ± 10 yr, who were receiving TSH suppressive doses of L-T_4 for thyroid cancer, were evaluated by Shapiro *et al.* (390). In this study TSH was suppressed to near the limits of assay detection (<0.01), and the mean serum T_4 and FT4 levels were significantly increased compared with the control group, although the mean serum level of FT3 was similar in the two groups. These patients had minimal symptoms but a significantly greater symptom score than controls (SRS, 4 ± 3 *vs.* 2 ± 1 in controls; $P < 0.05$). However, symptomatic patients, who were already under treatment with beta-blocking drugs, were excluded from the evaluation. Two other studies reported significantly higher mean symptom scores in patients with exogenous SHyper than in controls (11.1 ± 0.2 *vs.* 4.2 ± 2.3, $P < 0.001$; and 9.6 ± 3.7 *vs.* 5.3 ± 2.6, $P < 0.01$) (391, 392). In one of these studies, the patients receiving TSH suppressive therapy were selected for the presence of palpitations, increased heart rate, as well as other symptoms mimicking exaggerated β-adrenergic activity (391). In both studies, the scores were higher mainly for symptoms mimicking exaggerated β-adrenergic activity. In these two studies, TSH was below the detection sensitivity of the method, which was 0.05 mIU/liter in the study by Biondi *et al.* (391) and 0.1 mIU/liter in the study by Mercuro *et al.* (392). FT4, but not FT3, was significantly higher in patients than in controls (<0.001) in both the studies, although only two patients in the study by Biondi *et al.* and five patients in the study by Mercuro *et al.* had total T_4 and FT4 levels that exceeded the upper limit of reference range. Although it could be argued that some of these subjects actually had "overt" exogenous hyperthyroidism, patients with differentiated thyroid cancer (DTC) who are receiving TSH suppressive therapy may sometimes have serum FT4 levels that are at the upper limit of normal range or frankly elevated (362). In fact, FT4 levels can be 10–25% higher when measured in specimens drawn within 3–4 h after the morning L-T_4 dose.

Schlote *et al.* (393) investigated subclinically hyperthyroid individuals selected from a working population. They evaluated signs and symptoms of hyperthyroidism, sleep quality, depression, ability to concentrate, anxiety, and other dimensions of well-being in 15 subjects with SHyper taking L-T_4 and in 27 euthyroid controls. Patients with exogenous SHyper had significantly higher total T_4 levels and more palpitations than controls, and they slept less. However, psychometric results revealed only a few differences between patients with SHyper and normal subjects with no significant difference in mood.

Psychological performance and quality of life were recently studied in 18 patients with DTC, aged 44 ± 13 yr, with TSH less than 0.1 mIU/liter during chronic TSH suppressive therapy (394). At baseline evaluation, most patients had elevated serum FT4 concentrations. Compared with healthy controls, patients with DTC had impairment of several indices: the total score, and the emotional, sleep, energy, and social items of the Nottingham Health Profile; the mental health, general health, and social function of the SF-36; and the total score on the Wais Digit Span ($P < 0.05$ for all comparisons). Quality of life and cognitive performance were comparable with those of euthyroid controls 4–7 d after L-T_4 withdrawal (when most patients had normal serum FT4 and free T_3 levels). Finally, in a very recent multicenter study, the SF-36 scores of 228 patients with DTC were found to be above those of normal U.S. adults in six of eight categories during L-T_4 therapy, with the exception of modestly lower scores on the general heath and mental health domains (395).

In conclusion, patients receiving TSH suppressive doses of L-T_4 may have symptoms and signs of thyroid hormone excess. The presence of these symptoms should be considered when deciding on the appropriate target TSH levels in patients with DTC. This is particularly important in patients with low risk DTC who require long-term L-T_4 therapy but may not require aggressive TSH suppression (362, 363).

2. Symptoms and quality of life in endogenous SHyper. The Wayne score (a clinical index of hyperthyroidism), has been used for the clinical evaluation of patients with endogenous SHyper. Stott *et al.* (382) reported that the mean Wayne score of 15 elderly patients (aged 61–90 yr) with endogenous SHyper and undetectable TSH was similar to that of patients with overt thyrotoxicosis and worse *vs.* normal subjects. Similar findings were obtained by Sgarbi *et al.* (396) in 10 patients with endogenous SHyper aged 16–72 yr: the Wayne clinical index was significantly greater in patients with endogenous SHyper than in controls and was significantly correlated with serum TSH.

The SRS and SF-36 were used to evaluate 23 patients with endogenous SHyper aged 43 ± 9 yr with undetectable TSH in comparison with euthyroid subjects (397). The mean SRS for thyrotoxic symptoms was significantly higher in patients than in controls. Moreover, quality of life was reduced according to the SF-36 mental and physical component scores, and the SRS were inversely correlated with the cumulative score of the mental and physical components. Similarly, Gulseren *et al.* (398) reported reduced mental and physical component scores in patients with SHyper *vs.* a control group.

In conclusion, in patients with endogenous SHyper, the symptoms and signs, when present, are usually much less severe and not as specific as they are in overt thyrotoxicosis. There is an increased prevalence of symptoms and signs of adrenergic overactivity, and palpitations are frequent in young and middle-aged patients. Similar to SHypo, the extent of symptoms of SHyper is likely related to age, the duration of hyperthyroidism, and the patient's individual sensitivity to thyroid hormone excess.

G. Subclinical hyperthyroidism, mood, and cognitive function

There is no general consensus about the prevalence of anxiety and depression in patients with SHyper. A study conducted with the Beck Anxiety Inventory showed that patients with SHyper had significantly higher anxiety scores than a euthyroid group (116). However, in another study, anxiety scores did not differ between patients with SHyper and controls (399).

A reduced feeling of well-being and feelings of fear, hostility, and inability to concentrate were reported in patients with SHyper or previously treated hyperthyroidism (400). The study included patients with "remitted" hyperthyroidism, and it was observed that even after a long period of euthyroidism, neither the psychopathological nor the neuropsychological state became completely normal. Oomen *et al*. (401) evaluated thyroid function in all patients admitted to three psychiatric hospital in The Netherlands and found that 4.1% had a serum level of TSH less than 0.4 mIU/liter. Affective disorders (particularly depression in females and mania in males) were more prevalent in patients who had a suppressed serum TSH (401). However, causal relations cannot be determined from this cross-sectional study because suppressed TSH concentrations could be the consequence rather than a cause of the psychiatric illness and hospitalization.

In the population-based prospective Rotterdam study of 1846 persons over 55 yr of age, subjects with endogenous SHyper, defined by a serum TSH less than 0.4 mIU/liter at baseline, had a 3-fold increased risk of dementia and Alzheimer's disease (relative risk, 3.5) during 2–4 yr of follow-up (402). The risk of dementia was particularly increased in patients with positive antiperoxidase antibodies, hence the role of autoimmunity itself remains to be clarified. Similarly, in a case-control study there was a strong association between vascular dementia and low serum TSH defined as TSH of 0.5 mIU/liter or less (403). A low serum TSH concentration was associated with a 2-fold increased risk for Alzheimer's disease in another case-control study (404). However, in a cross-sectional investigation of 829 consecutive geriatric patients, no association was found between serum TSH levels and Alzheimer's disease (405). In a population-based cohort study of 1077 subjects aged 60–90 yr and dementia-free at baseline, with a follow-up of 5.5 yr, subjects with higher FT4 levels had more pronounced hippocampal and amygdalar atrophy on MRI (406). The functional significance of the association between higher FT4 levels with brain atrophy on MRI remains to be elucidated. Finally, in a recent community-based cross-sectional study of 127 persons aged 65 yr or older, SHyper was not associated with depression, anxiety, or cognition when compared with euthyroid subjects (117).

In summary, it is difficult to draw conclusions about the effects of SHyper on mood and cognitive function. Some confounding factors may interfere with this evaluation, *i.e*., the presence of autoimmunity and depression itself. It is difficult to establish whether TSH suppression, which is frequently associated with dementia, represents the cause or is a consequence of the disease. Moreover, patients identified by population screening may be less symptomatic than patients evaluated in clinical studies carried out to assess the effects of subclinical disease on symptoms.

H. Cardiovascular risk in subclinical hyperthyroidism

1. Cardiovascular effects of exogenous SHyper. It is noteworthy that the L-T_4 doses used to treat benign or malignant thyroid disease have progressively decreased over the years. In the decade 1970–1980, the daily dose of L-T_4 tended to be between 200 and 300 μg/d (407). In the 1970s, with the widely used L-T_4 dose of 150 μg/d, about 30% of treated subjects had raised serum T_4 levels (408, 409). At that time, a lack of serum TSH response to TRH was a common finding in patients taking T_4 replacement therapy (410). Decreased systolic time intervals, typical of hyperthyroidism, increased levels of glutathione-S-transferase, sex hormone binding protein and angiotensin-converting enzyme, alanine aminotransferase, and γ-glutamine transferase were reported in hypothyroid patients overtreated during T_4 replacement therapy, which indicated "tissue thyrotoxicosis" (411, 412). The adverse effects of this high L-T_4 dosage were attributed, in these early studies, to increased FT4 levels. In subsequent years, highly sensitive TSH assays allowed a more accurate adjustment of L-T_4 replacement therapy (413). However, adverse cardiac effects (shortened interventricular conduction time and PEP) were reported also in patients with normal free thyroid hormones but fully suppressed serum TSH (144). This was the first evidence that TSH suppression was indicative of thyroid hormone excess in peripheral target tissues (144), and it prompted studies of the effects of TSH suppressive therapy on the cardiovascular system.

The cardiovascular risk in patients with exogenous SHyper is related to the effects that can occur after brief exposure to thyroid hormone excess due to the electrophysiological action of the hormone (4, 414). T_3 increases the systolic depolarization and diastolic repolarization rate and decreases the action potential duration and the refractory period of the atrial myocardium as well as the atrial/ventricular nodal refractory period (415). Atrial arrhythmias (sinus tachycardia, atrial premature beats, and AF) are frequent complications of overt hyperthyroidism (121, 122, 136). In an attempt to evaluate the cardiac effects of SHyper, heart rate was monitored by 24-h ECG in four studies performed in patients receiving long-term TSH suppressive doses of L-T_4 (390, 416–418) (Table 13). A significant increase in the average heart rate, compared with controls, was identified in three studies of patients with exogenous SHyper (416–418). In two of these studies by Biondi *et al.* (417, 418) serum TSH was undetectable (TSH $<$ 0.05 mIU/liter) in patients receiving long-term therapy for benign or malignant disease, whereas TSH was

TABLE 13. Heart rate in patients with exogenous SHyper

Author	No. of patients	Method	SHyper	Heart rate
Bell, 1983 (416)[a]	7	Holter ECG	Suppressed TSH after TRH	↑
Biondi, 1993 (417)[b]	20	Holter ECG	<0.05 mIU/liter	↑
Biondi, 1999 (418)[b]	60	Holter ECG	<0.05 mIU/liter	↑
Shapiro, 1997 (390)[b]	17	Holter ECG	<0.01 mIU/liter	↔
Ching, 1996 (419)[b]	11	Ambulatory monitoring of pulse and blood pressure	<0.05 mIU/liter	↔

[a] Results before *vs.* after L-T_4 therapy.
[b] Results compared to euthyroid controls.

suppressed after TRH in the study by Bell *et al.* (416) of normal subjects after 24 d of L-T_4 administration. TSH was fully suppressed, and FT4 was at the upper limit of normal range and was significantly increased *vs.* the control group in two of these studies (417, 418). However, in another study of patients with the same hormonal pattern, the mean heart rate in exogenous SHyper patients was similar to that recorded in euthyroid subjects (390). Moreover, TSH suppressive doses of L-T_4 had no effect on 11 patients evaluated by Ching *et al.* (419) using ambulatory monitoring of pulse and blood pressure.

Atrial premature beats were not more frequent *vs.* controls in the patients in the study by Shapiro (390), but symptomatic patients receiving β-adrenergic receptors blockers were excluded from the cardiac evaluation. In contrast, in two studies, the prevalence of atrial premature beats was higher in young and middle-aged patients with exogenous SHyper than in a control group, and one young patient had a spontaneous run of AF (417, 418). Unfortunately, there have been no other studies of the prevalence of atrial arrhythmias in young and middle-aged patients with exogenous SHyper. However, four epidemiological studies showed an increased prevalence of AF in elderly patients with exogenous and endogenous SHyper (230, 375, 381, 420). The threshold for AF decreases with age, and the later diagnosis and coexistence of ischemic and degenerative heart disease likely predisposes elderly individuals to the development of AF in the presence of mild thyroid hormone excess.

Data on the electrophysiological action induced by L-T_4 suppressive therapy suggest that a standard ECG could be used to identify high-risk patients: those with a short P-R interval who are predisposed to reentrant atrioventricular nodal tachycardia (421) and those with higher maximum P wave duration and P wave dispersion who are predisposed to AF (422). In predisposed patients (those with two functionally distinct AV nodal conduction patterns), L-T_4 therapy may increase the occurrence of reentrant-atrioventricular nodal tachycardia because of the enhanced atrial excitability, which increases the number of atrial premature beats, and the shortening of the refractory period of the conducting tissue (421). Moreover, by measuring P maximum and P wave dispersion values, one could theoretically identify the patients with SHyper that are at high risk of AF (422). Holter ECG could be performed before starting L-T_4 treatment in doses that suppress TSH to potentially identify patients who may be less tolerant to L-T_4 treatment.

Long-term SHyper consequent to L-T_4 treatment can induce changes in cardiac morphology and function because of the increased cardiac workload (417, 418). Chronic hyperthyroidism induces cardiac hypertrophy in animal models (423). The mechanism of this hypertrophy is multifactorial and involves a direct effect exerted by thyroid hormone on the heart, indirect effects related to stimulation of the adrenergic nervous system or altered left ventricular loading conditions (increase in cardiac work), and local renin-angiotensin system activation (423–425). A significant increase in the left ventricular mass index (LVMI) has been documented in almost all studies of patients with exogenous SHyper compared with controls by Doppler echocardiography (390, 392, 417- 419, 426–428) (Table 14). The LVMI was not significantly higher in SHyper patients than in euthyroid controls in the study by Botella-Carretero *et al.* (429). However, the absence of significant cardiac structural changes in this study might be related to the shorter duration (a mean of approximately 4 yr) of TSH suppressive therapy compared with previous studies. Importantly, this study was the first to show that TSH suppressive T_4 therapy results in an increase in nighttime systolic and mean blood pressure (429). Interestingly, the increase in both interventricular septum and left ventricular posterior wall thickness, and consequently LVMI, was significantly greater in patients with symptoms and signs of adrenergic overactivity (SRS exceeded the mean value of the control group by more than 2

TABLE 14. LVMI in patients with exogenous SHyper in comparison with euthyroid control individuals

First author, year (Ref.)	No. of patients	LVMI	*P* value	TSH (mIU/liter)	Duration of L-T_4 treatment
Biondi, 1993 (417)	19	↑	<0.02	<0.05	5 ± 2.6 (1–9 yr)
Ching, 1996 (419)	11	↑	<0.01	<0.05	9.6 (3–21 yr)
Shapiro, 1997 (390)	17	↑	<0.05	<0.01	9.2 ± 5.4 (2.9–23 yr)
Biondi, 1999 (418)	60	↑	<0.001	<0.05	1–11 yr
Mercuro, 2000 (392)	23	↑	<0.01	0.05 ± 0.03	5.7 ± 3.5 (2–20 yr)
Botella-Carretero, 2004 (429)	21	↔		0.03 ± 0.03	~4 yr (47 ± 54 months)
Gullu, 2004 (426)	12	↑	<0.01	<0.05	>2 yr
	12			0.1–04	>2 yr
Smit, 2005 (427)	25	↑	0.1	<0.05–0.3	>10 yr
Shargorodsky, 2006 (428)	25	↑	<0.05	<0.05–0.3	3–21 yr

TSH values are mean ± SD.

SD) than in less symptomatic patients and normal subjects (391).

The clinical consequences of increased left ventricular mass in patients with SHyper remain to be established, although this increase is a negative prognostic factor for cardiovascular mortality and morbidity in the general population (430). In six studies, the increase in left ventricular mass was responsible for diastolic dysfunction, documented by Doppler echocardiography and radionuclide ventriculography (392, 418, 426, 427, 431, 432) (Table 15). Thyroid hormone excess exerts a beneficial effect on diastolic function. It affects the calcium-regulating proteins sarcoplasmic reticulum calcium-ATPase and phospholamban, thereby improving myocardial relaxation (120, 121). This beneficial effect of thyroid hormone excess is potentiated in hyperthyroid subjects by the enhanced ventricular suction effect (the atrial ventricular pressure gradient across the mitral valve) and the increased β-adrenergic stimulation (433). However, in long-term SHyper, the beneficial effects of thyroid hormone excess on diastolic function are counteracted by the concomitant ventricular hypertrophy induced by the chronically increased cardiac workload (Fig. 2). Indeed, the increase in the left ventricular mass was found to be significantly correlated with late diastolic filling (431).

Three studies investigated physical exercise capacity in SHyper patients (392, 432, 434). Impaired exercise tolerance was documented by means of cardiopulmonary exercise testing in symptomatic SHyper patients (392). Exercise tolerance, maximal VO_2 achieved at peak exercise, and anaerobic threshold were significantly reduced in patients receiving TSH suppressive doses of L-T_4. Plasma noradrenaline concentrations in patients who underwent the ergometabolic test were significantly lower in TSH suppressed patients in both the supine and standing position *vs.* euthyroid controls (392). In another study, maximal exercise capacity was greatly impaired in symptomatic patients with exogenous SHyper as documented by a significant reduction in peak workload and exercise duration during the bicycle ergometer test (432). Finally, radionuclide ventriculography has shown that the ejection fraction did not increase during exercise, but rather fell markedly below baseline in patients undergoing long-term TSH suppressive therapy (432). In both studies, there was a pronounced impairment of cardiac functional reserve and a reduction in physical exercise capacity in patients receiving TSH suppressive doses of L-T_4, which could impair quality of life (392, 432). In contrast, a recent study showed that exercise capacity evaluated by treadmill cardiopulmonary exercise test was not impaired in young and middle-aged female patients with exogenous SHyper (434).

In conclusion, the cardiovascular effects of exogenous SHyper are well documented in subjects with undetectable serum TSH. The major risk is represented by AF in elderly subjects. However, even in young and middle-aged patients, TSH suppressive doses of L-T_4 could impair quality of life by increasing heart rate and by reducing exercise capacity. Furthermore, long-term TSH suppression may increase the left ventricular mass. Although the consequences of this increase remain to be clarified, increased LVMI is a negative prognostic cardiovascular factor in the general population.

2. Cardiovascular effects of mild TSH suppression in exogenous SHyper. The serum TSH cutoff point that determines the adverse cardiac effects of SHyper remains to be established. Mercuro *et al.* (392) adjusted the L-T_4 dose in SHyper patients so that serum TSH rose from approximately 0.03 to 0.1 mIU/liter. All echocardiographic and ergometabolic parameters were improved after 6 months of "individual tailoring" of the TSH suppressive L-T_4 dose. Systolic indices were significantly decreased, and LVMI significantly improved in terms of interventricular septum and left ventricular posterior wall thickness. Diastolic function remained largely unchanged, although isovolumic relaxation time decreased. Moreover, L-T_4 dose adjustment induced a significant increase in maximal workload and maximum VO_2 at anaerobic threshold. Circulating noradrenaline, measured when the patient was supine or standing, was not significantly increased by customized L-T_4 doses (392).

Using Doppler echocardiography and the bicycle ergometer test, Gullu *et al.* (426) recently evaluated the effects of long-term TSH suppressive therapy (at least 2 yr) on cardiac function in patients with mild TSH suppression (serum TSH between 0.1 and 0.4 mIU/liter) and in patients with complete TSH suppression (serum TSH $<$ 0.05 mIU/liter). LVMI and isovolumic relaxation time were higher in patients with undetectable serum TSH than in patients with mild TSH suppression. Moreover, basal heart rate and the mean basal systolic blood pressure were higher in patients with undetectable serum TSH, and the baseline mean maximal exercise

TABLE 15. Diastolic function in patients with exogenous and endogenous SHyper in comparison with euthyroid control individuals

First author, year (Ref.)	No. of patients	Causes	Method	LV diastolic function
Fazio, 1995 (431)	25	Exo	Doppler echocardiography	↑ IRT, ↓ E/A
Biondi, 1996 (432)	10	Exo	Radionuclide ventriculography	↓ PFR
Shapiro, 1997 (390)	17	Exo	Doppler echocardiography	↔ E/A
Biondi, 1999 (418)	45	Exo	Doppler echocardiography	↑ IRT, ↓ E/A
Mercuro, 2000 (392)	19	Exo	Doppler echocardiography	↑ IRT, ↔ E/A
Biondi, 2003 (397)	23	Endo	Doppler echocardiography	↑ IRT, ↓ E/A
Petretta, 2001 (435)	30	Endo	Doppler echocardiography	↔ IRT, ↔ E/A
Gullu, 2004 (426)	12	Exo	Doppler echocardiography	↑ IRT ↓ E/A
Sgarbi, 2003 (396)	10	Endo	Doppler echocardiography	↑ IRT
Smit, 2005 (427)	25	Exo	Doppler echo, tissue Doppler	↑ IRT, ↓ E/A

IRT, Isovolumic relaxation time; PFR, peak filling rate; Exo, exogenous; Endo, endogenous; E/A, early-to-late transmitral peak flow velocity ratio.

P values for SHyper *vs.* control subjects: IRT, Mercuro, $P < 0.05$; Fazio and Smit, $P < 0.001$; Biondi 1999, $P < 0.01$; Biondi 2003, $P < 0.06$; Sgarbi, $P < 0.08$; Gullu, $P < 0.01$. E/A, Fazio and Smit, $P < 0.001$; Biondi 1999, $P < 0.01$; Biondi 2003, $P < 0.001$; Gullu, $P < 0.01$. PFR, Biondi 1996, $P < 0.005$.

time and the baseline peak workload were also higher in these patients than in patients with mild TSH suppression. However, even in patients with mild TSH suppression, the basal heart rate was higher and LVMI and isovolumic relaxation time were increased *vs.* an untreated healthy control group. LVMI was positively correlated with late diastolic flow velocity and negatively correlated with early diastolic flow velocity. Moreover, the baseline mean maximal exercise and the baseline peak workload were lower in patients with mild TSH suppression *vs.* controls. These results indicate that adverse cardiac effects may occur even when serum TSH is mildly suppressed (0.1–0.4 mIU/liter).

A prospective, randomized placebo-controlled study was carried out in athyreotic subjects with DTC receiving long-term TSH suppressive therapy (<10 yr) to assess the reversibility of the effects of exogenous SHyper on systolic and diastolic function (427). These low-risk patients were randomized to continue TSH suppressive therapy (target serum TSH level < 0.4 mIU/liter) or to a decreased L-T_4 dose to restore euthyroidism (target serum TSH within the normal range, 0.4–4.8 mIU/liter). At baseline, LVMI, interventricular septum, and left ventricular posterior wall thickness were higher in DTC patients than in controls, and four patients had left ventricular hypertrophy. Left ventricular ejection fraction and fractional shortening were lower in patients than in controls, and, diastolic dysfunction was documented in DTC patients by Doppler echocardiography and tissue Doppler imaging. After 6 months, in the euthyroid group, LVMI had not improved, whereas left ventricular ejection fraction, fractional shortening, left ventricular end diastolic dimensions, and diastolic function had. No change was observed in the low TSH group. The results of this study indicate that diastolic dysfunction due to long-term exogenous SHyper is reversible when euthyroidism is restored.

In conclusion, prospective studies are needed to clarify further the cardiovascular effects of mild TSH suppression induced by L-T_4. However, the available data support the hypothesis that the negative effects of complete TSH suppression are partly reversible by reducing the L-T_4 dosage. Studies with a longer follow-up can clarify whether these negative effects are fully reversible. The target serum TSH that will minimize negative cardiovascular effects remains to be established.

3. Cardiovascular effects of endogenous SHyper. The cardiovascular effects of endogenous SHyper are similar to those reported in exogenous SHyper. Five studies have evaluated the cardiovascular effects of stable endogenous SHyper using ECG and Doppler echocardiography (396, 397, 435–437). An increase in the average heart rate was found in three studies in which serum TSH was undetectable (396, 397, 435) (Table 16). Biondi *et al.* (397) reported a higher prevalence of atrial premature beats in patients with endogenous SHyper than in controls, although the difference was not significant. On the other hand, Sgarbi *et al.* (396) reported a significant increase in atrial and ventricular premature beats in patients with endogenous SHyper. They also found that TSH and FT4 levels correlated significantly with atrial and ventricular premature beats (396). However, in a study of patients with SHyper and detectable serum TSH, Holter ECG did not demonstrate differences in mean, minimal, and maximal heart rate between patients with endogenous SHyper due to multinodular goiter with serum TSH below 0.4 mIU/liter or above 0.4 mIU/liter and controls (436). Moreover, the frequency of atrial or ventricular premature beats did not differ among the groups studied. In another study, heart rate variability was analyzed to characterize autonomic control in patients with subclinical and overt hyperthyroidism (435). "Heart rate variability" has become the conventionally accepted term to describe variations of both instantaneous heart rate and RR intervals. In this study, the variations in heart rate were evaluated by the time domain measures (435). The procedure entails measurement of either the heart rate at any point in time or the intervals between successive normal complexes. In a continuous ECG record, each QRS complex is detected, and the so-called normal-to-normal (NN) interval (that is, all intervals between adjacent QRS complexes resulting from sinus node depolarizations) or the instantaneous heart rate is determined. This study showed that average NN intervals and all time and frequency domain measures decreased progressively from normal individuals to patients with endogenous SHyper and to patients with overt disease ($P < 0.001$). These data demonstrate a reduction in cardiac vagal control in SHyper—a finding that may have important clinical implications, because reduced heart rate variability may predict an increased risk for subsequent cardiac events in the general population (437).

Four studies have evaluated Doppler echocardiography findings in patients with endogenous SHyper (396, 397, 435, 438), and an increase in left ventricular mass was found in three studies (396, 397, 438) (Table 17). In the study by Tamer *et al.* (438), mild or moderately hypertensive patients with endogenous SHyper had a greater increase in left ventricular mass compared with mild or moderately hypertensive subjects without SHyper, which suggests that persistent SHyper may further increase the cardiovascular risk associated with hypertension. An increase in left ventricular mass was not found in one study (435), and altered diastolic function was found in two studies (396, 397) (Table 15).

In a recent population-based study involving 1510 individuals aged 45–79 yr in Pomerania (439), SHyper was not

TABLE 16. Heart rate (HR) in patients with endogenous SHyper in comparison with euthyroid control individuals

First author, year (Ref.)	No. of patients	Methods	HR	TSH (mIU/liter)
Biondi, 2003 (397)	23	Holter ECG	↑	0.16 ± 0.11
Petretta, 2001 (435)	30	HRV	HRV ↓	0.05 ± 0.07
Sgarbi, 2003 (396)	10	Holter ECG	↑	0.05 ± 0.03
Berghout, 2003 (436)	26	Holter ECG	↔	0.6 ± 0.4

TSH values are mean ± SD. HRV, Heart rate variability.

TABLE 17. LVMI in patients with endogenous SHyper in comparison with euthyroid control individuals

First author, year (Ref.)	No. of patients	Methods	LVMI	*P vs.* controls	TSH (mIU/liter)
Biondi, 2003 (397)	23	Doppler echo	↑	<0.001	0.16 ± 0.11
Petretta, 2001 (435)[a]	30	Doppler echo	↔		0.05 ± 0.07
Sgarbi, 2003 (396)	10	Doppler echo	↑	0.02	0.05 ± 0.03
Tamer, 2005 (438)[b]	16	Doppler echo	↑	<0.01	0.15 ± 0.1

TSH values are mean ± SD.
[a] 6 Grave's disease, 14 thyroid autonomy, 10 multimodular goiter.
[b] Hypertensive patients with endogenous SHyper.

associated with left ventricular hypertrophy, whereas a positive association was found between overt hyperthyroidism and left ventricular hypertrophy. Logistic regression analysis showed that hyperthyroidism was an independent risk factor for left ventricular hypertrophy. However, this population-based study did not examine patients with known thyroid disorders, who were excluded from the evaluation. On this basis, the subjects with decreased TSH levels that were identified may correspond to individuals with an earlier stage of SHyper (439).

In the population-based health study carried out in Pomerania, the analysis of data from 2086 individuals at least 45 yr old with carotid ultrasound and without known thyroid disorders revealed a linear relationship between thyroid function and CIMT (440). Subjects with decreased serum TSH levels and overt hyperthyroid individuals had higher IMT values than subjects with elevated serum TSH levels. This relationship remained statistically significant after appropriate adjustment for known IMT risk factors. Moreover, subjects with low serum TSH levels had higher IMT values than subjects with serum TSH levels within the second and the third quartile of TSH distribution. It was suggested that the increase in IMT in the common carotid artery was related to medial hypertrophy rather than to true intimal atherosclerosis. In another study, no difference was found in flow-mediated dilatation in SHyper *vs.* euthyroid subjects (441).

Finally, in the population-based study of health in Pomerania that included 4310 subjects aged 20–79 yr, thyroid function status was found to be associated with plasma fibrinogen concentration (442), and decreased serum TSH was an independent risk factor for elevated plasma fibrinogen levels. Increased factor X activity was recently found in patients with SHyper, but it is unknown whether the increased factor X levels in the range reported could induce a hypercoagulable state (443). This situation might be particularly dangerous in subjects with SHyper who are more prone to develop AF because of the increased risk of embolic events.

In conclusion, some important cardiovascular risk factors could be associated with endogenous SHyper: increased heart rate, increased risk for atrial arrhythmias, reduced heart rate variability, and increased left ventricular mass. It remains to be established whether these cardiovascular risks could be responsible for the increased cardiovascular mortality reported in some studies. Additional studies are required to determine whether these cardiovascular risk factors can be reversed by appropriate treatment.

4. Epidemiological cardiovascular studies. Cardiovascular morbidity and mortality in patients with exogenous and endogenous SHyper have been investigated in several epidemiological studies (Table 18). The first study was carried out in 1990. Twenty-nine women treated with L-T_4 from one to 28 yr were identified from among a Swedish population of 1462 middle-aged women and were investigated for the risk of myocardial infarction, diabetes mellitus, stroke, cancer, and death (444). The 12-yr follow-up of this small number of patients treated with L-T_4 in 1968 and 1969 did not indicate any increase in morbidity or mortality. However, the results of this study should be viewed in the light of the heterogeneity of the patients receiving L-T_4 (seven patients for spontaneous hypothyroidism, five for euthyroid nodular goiter after surgery, five after surgery for thyrotoxicosis, five for euthyroid goiter, and two for other indications). Moreover, although FT3 was defined as being in the normal range, data about FT4 values and the degree of TSH suppression were not reported.

In 1992, Leese *et al.* (445) examined 1180 patients aged 38 to 60 yr on L-T_4 replacement therapy who were recalled for clinical and biochemical assessment. Ninety percent were female, 75% of these were over 50 yr of age, and 40% were over 65 yr of age; 51% were originally thyrotoxic, and 49% had primary hypothyroidism. Patients on L-T_4 with suppressed TSH (<0.05 mIU/liter; 59%) were compared with those in whom TSH was detectable (0.05–4.0 mIU/liter; 38%). Overall hospital admission rates of L-T_4-treated patients were identical in those with normal serum TSH (48%) and those with suppressed serum TSH (47%). Although patients under the age of 55 yr on L-T_4 had an increased risk of ischemic heart disease compared with the general population, this risk did not differ between women with fully suppressed TSH and those with TSH between 0.05 and 4.0 mIU/liter.

Various studies have identified an increased risk of AF in older patients with SHyper (230, 375, 381, 420). Tenerz *et al.* (381) reported the results of a 2-yr follow-up investigation that included 40 patients with subclinical thyrotoxicosis and 40 euthyroid control subjects. Twelve (30%) of the patients but none of the individuals in the control group were treated during the follow-up period for clinical thyroid disease. AF was found in 11 (28%) patients compared with four (10%) of the controls. Patients with endogenous SHyper, defined by a TSH serum level below 0.1 mIU/liter (mean age, 65 yr), had a 2.8-fold increased risk of AF over 2 yr compared with aged-matched euthyroid controls.

In a prospective study, 2007 people 60 yr or older who did not have AF at the start of the study were examined to determine the frequency of this arrhythmia during a 10-yr follow-up period (375). Subjects were classified according to their serum TSH concentration: low values (≤0.1 mIU/liter;

TABLE 18. Association between SHyper and cardiovascular risk: epidemiological evidence

First author, year (Ref.)	No. of patients	Sex	TSH	Age (yr)	Follow-up (yr)	Cardiovascular risk
Petersen, 1990 (444)	1,462 (29 exo SHyper)	W		38–60	12	No increased risk in morbidity and mortality
Leese, 1992 (445)	1,180 exo SHyper	W and M	<0.05 in 59%	45–64	5	Increased risk of IHD
Sawin, 1994 (375)	2007 exo and endo SHyper	W-M	<0.1	≥60	10	No increased cardiovascular mortality; 3-fold higher incidence of AF
			0.1–0.4			No risk of AF and mortality
Parle, 2001 (229)	1,191 (71 with endo SHyper)	W and M	<0.5	≥60	10	Increased mortality from circulatory disease in yr 2–5
Auer, 2001 (420)	23,638 (613 with endo SHyper)	W and M	<0.4	≥45	From 1986–1995	>5-fold higher risk of AF
Gussekloo, 2004 (92)	599 (17 with low TSH)	W and M	<0.3	85–89	4	Increased cardiac mortality
Walsh, 2005 (38)	2108 (39 with SHyper)	W and M	<0.1; 0.1–0.4	51.3 ± 14.9	20	No increased mortality (either cardiovascular or total)
van den Beld, 2005 (314)	442 with SHyper	W and M	<0.4	73–94	4	No increased mortality
Cappola, 2006 (230)	3233 (47 with endo SHyper)	W and M	0.10–0.40; <0.1	73.9 ± 6.8	13	No increased cardiovascular death or all causes of death; increased risk of AF

Data are reported as mean ± SD. exo, Exogenous; endo, endogenous; IHD, ischemic heart disease; M, men; W, women; AF, atrial fibrillation.

61 subjects), slightly low values (< 0.1 to 0.4 mIU/liter; 187 subjects), normal values (>0.4 to 5.0 mIU/liter; 1576 subjects), and high values (>5 mIU/liter; 183 subjects). During the 10-yr follow-up, 192 subjects (10%) developed AF. The cumulative incidence of AF at 10 yr among subjects with a low TSH was 28% *vs.* 11% among those with normal TSH ($P = 0.005$). The incidence of AF did not differ between subjects with a slightly low TSH and the normal TSH group (16 *vs.* 15%). After adjustment for other known risk factors, the relative risk for AF was 3.1 for subjects with low TSH ($P < 0.001$) and 1.6 for those with slightly low TSH ($P = 0.05$) *vs.* those with normal TSH. There was no increased mortality associated with SHyper over the course of 10 yr.

Auer *et al.* (420) carried out a retrospective study of 23,638 subjects to evaluate the risk of AF in overt and subclinical hyperthyroidism. The evaluation was performed on 1338 consecutive patients with low TSH (85% with functional thyroid autonomy, 15% with Graves' disease), of whom 725 patients had overt hyperthyroidism and 613 had SHyper (TSH < 0.4 mIU/liter). The pool of patients comprised all consecutive patients referred for thyroid function testing for different reasons (screening, suspected thyroid disease, concomitant disease). The control group consisted of 22,300 euthyroid people at least 45 yr old who were admitted to the institution between 1989 and 1994. AF was present in 2.3% of people with normal thyroid function, in 13.8% of patients with overt hyperthyroidism, and in 12.7% of patients with SHyper. A low serum TSH was associated with a greater than 5-fold higher likelihood of AF, with no significant difference between overt and SHyper patients. Although the patients in this study had a high prevalence of underlying heart disease (coronary artery disease, dilated cardiomyopathy, valvular heart disease, or a combination of these), when the results were adjusted for age and for the presence of other known risk factors for AF (hypertension, left ventricular hypertrophy, and underlying heart disease), the relative risk of AF in subjects with SHyper remained significantly different ($P < 0.01$) from those with normal serum TSH (relative risk, 2.8).

A recent study by Cappola *et al.* (230) confirmed these data on the risk of AF in SHyper patients. They evaluated 496 patients with a mean age of 73 yr (15% of the study population) with SHyper (mean age, 72.7 yr) and 2639 subjects (82%) with normal thyroid function to determine the relationship between baseline thyroid status and incident AF, cardiovascular disease, and mortality. SHyper was defined as a serum TSH concentration of 0.10–0.44 mIU/liter (n = 40) or less than 0.10 mIU/liter with a normal FT4 concentration (n = 7). During a 13-yr follow-up, the incidence of AF was greater in individuals with SHyper than in the euthyroid group, with 67 *vs.* 31 events per 1000 person-years ($P < 0.001$). After adjustment for age, sex, clinical cardiovascular disease at baseline, subsequent medication use, and other known risk factors for AF, subjects with SHyper had nearly twice the risk of developing AF. The incidence rate of AF in the subgroup of patients with a serum TSH concentration between 0.1 and 0.44 mIU/liter was 59 per 1000 person-years ($P = 0.007$ *vs.* the euthyroid group). Mortality was significantly higher in patients with SHyper (58.1 *vs.* 34.2 events per 1000 person-years; $P = 0.02$), which disappeared after adjustment for age and sex ($P = 0.29$). No differences in other

clinical cardiovascular conditions were observed in this study.

Parle *et al.* (229) carried out a community-based review of subjects with SHyper monitored for 10 yr to define the cardiovascular risk associated with endogenous subclinical disease. A total of 1191 subjects age 60 and older who were not receiving T_4 therapy or antithyroid medication were evaluated. Serum TSH was measured at baseline in 1988–89. At the time of blood sampling, 70 individuals had SHyper, of whom 69 were in sinus rhythm and one had AF. Causes of death were identified for subjects who died after the follow-up and were compared with age, gender, and specific data for England and Wales. All-cause mortality was found to be significantly increased 2, 3, 4, and 5 yr after initial measurement in subjects with low serum TSH concentrations (≤0.5 mIU/liter; n = 71) compared with the expected mortality for the control population. The increase in all-cause mortality was due to a significant increase in mortality because of circulatory diseases and, specifically, cardiovascular diseases. There was no significant difference in survival between subjects with serum TSH 0.1–0.4 mIU/liter *vs.* serum TSH less than 0.1 mIU/liter. Although the underlying cause of the reduced TSH value was not investigated in this cohort, certain findings support the hypothesis that the low TSH concentration was due to true endogenous mild SHyper rather than to such other causes as drug treatment or nonthyroidal illnesses (446). For example, the mean serum concentration of free thyroid hormone was inversely related to serum TSH in this cohort. Moreover, many patients had clinical features of thyroid disease, *e.g.*, goiter. Furthermore, common causes of death, other than vascular causes, were not associated with low serum TSH, which would be expected if serum TSH were a nonspecific reflection of other illnesses (446).

In the study by Gussekloo *et al*. (92) of a cohort of subjects over age 85 yr, increased cardiovascular mortality was observed during 4 yr of follow-up in 17 subjects with low levels of TSH at baseline evaluation. Moreover, higher levels of FT4 were associated with an increased risk of cardiovascular and noncardiovascular mortality (92). van den Beld *et al.* (314) also reported that higher FT4 levels within the normal range (independent of TSH levels) were associated with a higher risk of 4-yr mortality in subjects aged 73 to 94 yr. However, in this study, 444 subclinically hyperthyroid subjects did not have a higher 4-yr mortality than euthyroid subjects. Finally, Walsh *et al*. (38) recently assessed the risk for cardiovascular disease in SCTD in 2108 subjects during a 20-yr follow-up. SHyper was defined as a serum TSH serum level of 0.02–0.40 mIU/liter and was found in 39 patients (prevalence, 1.8%), whose mean age was 51.3 ± 14.9 yr. Subjects with SHyper had no adverse outcomes and no evidence of increased cardiovascular risk. There was no significant increase of coronary heart disease events in the group of subjects with SHyper or in the subgroups with TSH less than 0.1 mIU/liter and between 0.1 and 0.4 mIU/liter. These results are in contrast to those reported in older patients by Parle *et al.* (229). Unfortunately, AF was not evaluated in this study.

In conclusion, conflicting results emerge from epidemiological studies on cardiovascular mortality in SHyper. Similar to the studies performed in SHypo patients, subjects in studies of SHyper differ with respect to the etiology of condition (exogenous or endogenous), age and sex, disease duration, and duration of follow-up. Very few analyses were adjusted for age, sex, and race. Some patients may have progressed to overt disease during the follow-up, and this is particularly true for studies in which only one serum TSH evaluation was performed at baseline evaluation. Moreover, some studies evaluated TSH alone without concomitant thyroid hormone assessment, so that overt hyperthyroidism cannot be ruled out. Nevertheless, the evidence strongly indicates that there is a higher risk of AF in elderly persons with SHyper, and it supports the concept that treatment should be considered in this group.

I. Subclinical hyperthyroidism and bone and mineral metabolism

Thyroid hormone excess is associated with accelerated bone remodeling, thereby leading to a negative calcium balance and a net bone loss (447, 448). Overt hyperthyroidism is an important risk factor for osteoporosis and fractures (449, 450). It is still a matter of debate whether persistent SHyper can affect bone metabolism and increase the risk of fractures. In experimental animals, T_4 excess caused osteopenia, which is more pronounced in cortical bone than in trabecular bone (451). Conflicting results have been reported concerning the serum concentration of osteocalcin, a marker of bone formation, in both endogenous and exogenous SHyper (452-458). A weak negative correlation was seen between serum TSH and serum levels of osteocalcin in three studies (452, 456, 458). Elevated urinary excretion of bone collagen, urinary pyridinoline cross-links, and hydroxyproline was reported in postmenopausal women with SHyper (459), and telopeptide type I, a marker of bone resorption, was slightly but significantly increased in patients with SHyper (460).

Thyroid hormones affect bone remodeling in patients with thyroid disease by acting directly or indirectly on osteoclast activity. TSH may also affect skeletal remodeling by interacting with the specific receptors expressed on bone cells (461). In experimental animals, the reduced expression of the TSH receptor leads to the development of osteoporosis, which raises the possibility that the effect of TSH suppression on bone turnover could be mediated by TSH deficiency rather than by thyroid hormone excess (461). Although the osteoporosis associated with hyperthyroidism is traditionally viewed as a secondary consequence of altered thyroid function, these data provide experimental evidence that TSH directly affects both osteoblastic bone formation and osteoclastic bone resorption.

The effects of exogenous and endogenous SHyper on BMD and the risk of fractures in pre- and postmenopausal women have been widely studied. However, it should be stressed that the criteria used to select patients and controls were not very stringent in the early studies. Similarly, techniques that accurately measure BMD have only recently become available.

1. Effects of exogenous SHyper on BMD. Studies of the effects of thyroid hormone suppressive therapy in premenopausal women have yielded conflicting results. Early cross-sectional

studies of bone resorption in premenopausal women showed reduced bone density in the femoral neck and forearm but not of the lumbar spine as measured by single-photon absorptiometry and dual-photon absorptiometry (462–465). However, at that time, high doses of L-T_4 or T_3 were used to suppress TSH, leading to iatrogenic hyperthyroidism and not SHyper in many instances. In addition, patients with a history of hyperthyroidism were included in the evaluation of BMD. In subsequent cross-sectional studies, L-T_4 did not have significant adverse effects on bone in men (466–468) or in premenopausal women (467–477). Over the last 15–20 yr, lower L-T_4 doses have been used to obtain mild TSH suppression, especially in patients with benign thyroid disease. This could explain the differences in BMD data between earlier and more recent studies and suggest that a lesser degree of TSH suppression can minimize the risk of osteoporosis.

Longitudinal studies of premenopausal women receiving suppressive doses of L-T_4 report a decrease in BMD of the spine or forearm (478–480) or no significant adverse effects on bone (481, 482). The different durations of follow-up in these longitudinal studies could account for the conflicting findings. Similarly, conflicting data have been reported for postmenopausal women with SHyper. BMD was decreased in postmenopausal women with exogenous SHyper in several cross-sectional (483–488) and longitudinal studies (481, 489). However, exogenous SHyper had no significant adverse effects on BMD in postmenopausal women in other cross-sectional (467, 468, 470–472) and longitudinal (456, 481, 490, 491) studies.

Two meta-analyses of patients with exogenous SHyper (combining 13 and 41 cross-sectional studies, respectively), assessed the effects of L-T_4 suppressive therapy in pre- and postmenopausal women (492, 493). In neither study was L-T_4 therapy shown to adversely affect BMD in premenopausal women. However, in postmenopausal women, there was a loss of 0.77–1.39% in bone mineral per year, which was a significant reduction compared with controls (492). Moreover, there was an excess annual loss of 0.91% per year after 9.9 yr in postmenopausal women compared with normal controls (493). Cortical bone was more affected than trabecular bone.

The effects of TSH suppression on BMD are controversial in patients with DTC (494–495). The effects of TSH suppression may be more pronounced in patients with DTC because they undergo constant and long-term TSH suppression. In a recent overview (494), it was found that there was no change or only a small decrease in BMD as a result of long-term TSH suppressive therapy (mean, 7.1 yr in eight trials) in premenopausal women with DTC. However, the findings for postmenopausal women remain unclear, with two of the best controlled studies reporting opposing results (467, 489). However, dietary calcium intake differed in the two studies, being higher in the study by Franklyn *et al.* (467). In contrast, a recent cross-sectional study of 66 DTC patients in pre- and postmenopausal status showed that 28 postmenopausal patients had higher values of the C-telopeptide of type 1 collagen and bone alkaline phosphatase and lower BMD values than healthy subjects (496).

Heemstra *et al.* (495) recently examined 21 studies of patients with DTC receiving long-term TSH suppressive therapy; the studies were stratified according to gender and menopausal status. The results showed that TSH suppressive therapy did not affect BMD in men or in premenopausal women, whereas postmenopausal patients were at risk of bone loss.

Conflicting data have also been reported in longitudinal studies (480, 490–491). A bone loss of 6.7% in the hip after 2 yr of follow-up was also found in the study by Kung and Yeung (497) of 15 postmenopausal women with DTC. However, in one study, long-term TSH suppressive therapy in 59 patients with DTC did not result in reduced BMD of the hip in pre- and postmenopausal women, or in men (498). BMD, expressed as Z score, was not correlated with duration of L-T_4 therapy, and even in patients who had undergone suppressive therapy for more 10 yr there was no significant decrease in BMD. Moreover, long-term TSH suppressive therapy with L-T_4 (12 ± 5 yr) did not affect skeletal integrity in 88 pre- and postmenopausal women with DTC in another study by Reverter *et al.* (499).

In conclusion, TSH suppression induced by L-T_4 therapy probably does not affect BMD in premenopausal women or men, although conflicting findings were obtained concerning patients with DTC. In postmenopausal patients, L-T_4 may accelerate bone turnover, depending on the degree of serum TSH suppression and dietary calcium intake.

2. Effects of endogenous SHyper on BMD. Data about BMD in patients with endogenous SHyper differ from study to study (454, 455, 500–505). Three studies found that endogenous SHyper did not affect BMD in premenopausal patients (454, 455, 500). In contrast, in two studies of postmenopausal women, forearm bone density was decreased (501, 502). In a case-control study of 37 pre- and postmenopausal women with SHyper, the bone densities of the lumbar spine, femoral neck, and the midshaft of the radius were not significantly decreased in premenopausal patients with endogenous SHyper due to solitary AFTN. However, decreased BMD was observed in postmenopausal women (503). Sites rich in cortical bone were preferentially affected. Kumeda *et al.* (504) assessed bone metabolism in 19 premenopausal patients with SHyper due to Graves' disease *vs.* 30 premenopausal Graves' disease patients with normal serum TSH levels. Concentrations of serum and urine bone turnover markers were significantly higher in patients with persistent TSH suppression than in women with normal serum TSH values, which suggests that it may be important to achieve normalization of TSH levels during antithyroid therapy so as to normalize bone turnover. In a study in men, BMD was reduced, and levels of osteocalcin and alkaline phosphatase were increased in 49 patients, 32 with recent onset overt and SHyper due to Graves' disease, and 17 receiving TSH suppressive therapy when compared with treated (but euthyroid) Graves' patients, confirming the data reported for women (505).

In conclusion, the effects of endogenous SHyper are likely influenced by the duration of the disease and associated risk factors for bone loss (4). The major problem in assessing the adverse skeletal effects of endogenous SHyper is the difficulty in establishing disease duration. Thus, studies carried

out to evaluate BMD may have compared patients who had different disease durations. Although only a few studies have been performed and the numbers of patients with endogenous SHyper were small, the results support the hypothesis that SHyper can cause reduced BMD, particularly in cortical bone.

3. SHyper and risk of fractures. Few studies have evaluated whether SHyper increases the risk of fractures. Solomon *et al.* (506) interviewed 300 white postmenopausal women (160 with thyroid disease and 140 without thyroid disease) to investigate whether having thyroid disease or taking thyroid hormone increased the prevalence of having a hip, vertebral, or forearm fracture. Thirty-seven (23%) women with thyroid disease and 45 (32%) women without thyroid disease had a fracture. There were no significant differences between these groups in the number or type of fractures. Moreover, the dose of thyroid hormone and duration of therapy or disease did not affect fracture occurrence in women with thyroid disease. However, women with a history of hyperthyroidism (9 of 32) or thyroid cancer (2 of 11) appeared to have their first fracture earlier ($P < 0.01$) than women without thyroid disease (506).

Three studies have evaluated the risk of fracture in patients with low serum TSH. In a study of 1180 patients receiving L-T_4 (of whom 59% had a low TSH concentration), the overall fracture rate after 5 yr was 2.5% in women over age 65 yr with a low TSH concentration and 0.9% in those with normal TSH values; the difference was not significant (445). Sheppard *et al.* (507) conducted a population-based, case-control analysis of the risk of a femoral fracture in a large cohort of patients from the United Kingdom who had been prescribed L-T_4. No association between fracture and L-T_4 prescription was found. Femoral fracture was significantly associated with L-T_4 therapy in males, but not in women, after correction for other confounding risk factors. However, this study did not evaluate patients with low TSH *vs.* patients with normal TSH (507). Bauer *et al.* (508), in a prospective cohort study with case-cohort sampling, evaluated the risk of fractures in 686 women older than 65 yr with low serum TSH from a cohort of 9704 women recruited between 1986 and 1988 from the population-based listings at four clinical centers. The study included women with exogenous and endogenous SHyper. After adjustment for age, history of hyperthyroidism, and use of estrogen and thyroid hormone, women with a serum TSH level of 0.1 mIU/liter or less had a 3-fold increased risk of hip fracture and a 4-fold increased risk of vertebral fracture compared with women who had normal serum TSH levels. Women receiving L-T_4 doses to maintain TSH in the range of 0.1–0.5 mIU/liter did have an increased risk of fracture. However, data on FT4 or FT3 levels in the population were not reported. Therefore, it is unknown whether the patients with low serum TSH levels had SHyper or more severe hyperthyroidism.

In conclusion, confounding factors may have affected the results of studies about fracture risk in SHyper. Moreover, in some studies, patients with overt disease were included in the evaluation. It remains to be clarified whether or not a risk of fracture is associated with SHyper and, should this be the case, to be determined at which serum TSH level this risk occurs.

J. Effects of treatment

1. Effect of treatment on quality of life. Few studies have evaluated whether treatment of exogenous or endogenous SHyper improves quality of life and thyrotoxic symptoms. An improvement in quality of life was identified by means of the SRS after the addition of a beta-blocking drug to L-T_4 treatment in 11 patients with symptoms and signs of adrenergic overactivity (391). The SRS significantly decreased from 11.1 ± 5 to 5.4 ± 3 after 6 months of bisoprolol treatment. Individual titration of the L-T_4 dose to the minimal amount able to keep serum TSH concentration at 0.1 mIU/liter or less in seven symptomatic patients with exogenous SHyper was associated with a significant improvement in the thyrotoxic score 6 months after the initial evaluation (from 12.8 ± 2 to 9.9 ± 3; $P < 0.005$). However, although the symptom score improved in treated patients, it still differed significantly *vs.* controls (9.2 ± 3 *vs.* 5.3 ± 3) (392). Moreover, the Wayne clinical index was significantly reduced in 10 patients with endogenous SHyper who had reached the euthyroid state after methimazole treatment (396).

Quality of life was recently evaluated in 24 subjects with DTC receiving long-term TSH suppressive therapy to determine the effects of restoration of euthyroidism (509). The study was a prospective, single-blinded randomized controlled study of 6-month duration with two parallel groups. After inclusion, patients were randomized to continue TSH suppressive therapy (low-TSH group with target serum TSH level < 0.4 mIU/liter) or restoration of euthyroidism by decreasing the L-T_4 dose (euthyroid group target serum TSH levels within the normal reference range, 0.4–4.8 mIU/liter). At baseline, the somatic disorder questionnaire showed greater somatic dysfunction in patients with DTC, whereas depression was less than in the reference group. All other quality of life parameters were normal. After 6 months, none of the quality of life parameters in the low TSH group differed from baseline values. In the euthyroid group, motivation was significantly improved, and there was no improvement in somatic disorder questionnaire score. This study suggests that quality of life is preserved in patients with DTC, with no further improvement after restoration of euthyroidism.

In conclusion, a lesser degree of TSH suppression may improve quality of life in exogenous SHyper (392), and beta-blocking drugs can be useful in patients complaining of symptoms and signs of adrenergic overactivity (391). Antithyroid drugs have been reported to improve quality of life in patients affected by endogenous SHyper (396); however, this finding should be verified in other studies.

2. Is it possible to reduce the cardiovascular risk induced by exogenous SHyper? The addition of propranolol to T_4 prevented both the increased heart rate and the hypertrophic response in hyperthyroid rats (510). In patients with exogenous SHyper, the administration of a beta-blocking drug reduced the increased heart rate and left ventricular mass, thereby improving diastolic and systolic function during exercise (391, 431, 432). In the first of these studies, bisopropol, a cardioselective beta-blocking drug with a long half-life, was added to L-T_4 suppressive therapy (TSH < 0.05 mIU/liter) in 11 patients affected by palpitations, increased heart rate, and

other symptoms mimicking exaggerated β-adrenergic activity (391). The addition of bisoprolol to L-T_4 suppressive therapy produced normalization of heart rate and disappearance of atrial arrhythmias. After 6 months of L-T_4 plus bisoprolol therapy, the LVMI normalized, the indices of left ventricular systolic function were reduced, and there was a tendency to normalization. Also diastolic dysfunction, cardiac performance, and exercise tolerance were significantly improved by adrenergic beta-blockade (431, 432).

In a study by Gullu *et al.* (426), atenolol at a dosage of 50 mg/d for 3 months was given to patients receiving mild TSH suppressive therapy (TSH 0.1–04 mIU/liter). There was no statistically significant improvement in LVMI and diastolic function after atenolol therapy. However, both the mean maximal exercise time and peak workload increased during β-adrenergic blockade. This study confirms that beta-blockade improves cardiac function in patients with mild TSH suppression even after short-term administration of a beta-blocker. Both of these studies support the idea that β-adrenergic blocking drugs should reduce the cardiovascular risk, and thus they might be considered for patients requiring long-term TSH suppressive therapy, especially symptomatic patients with high-risk thyroid cancer in which more aggressive TSH suppression may be required.

3. Is it possible to reduce the cardiovascular risk induced by endogenous SHyper? Two studies have assessed the cardiovascular effects of normalization of serum TSH concentration in patients with endogenous SHyper after antithyroid drugs and radioiodine, respectively (396, 511). Ten patients, median age 59 yr, were reevaluated by Holter ECG and Doppler echocardiography after 6 months of methimazole treatment with a median dose of 20 mg/d to achieve stable euthyroidism (396). Heart rate and the number of atrial and ventricular premature beats were significantly reduced when euthyroidism was reached and were similar to those recorded in euthyroid controls. The LVMI was significantly reduced after methimazole treatment, and it became similar to that of the control group. The thyrotoxic symptom score improved after therapy, although it remained significantly higher in SHyper patients than controls (396). In another study, radioiodine treatment given to normalize serum TSH in six subclinical hyperthyroid women with multinodular goiter resulted in an 11% reduction in heart rate, a 19% reduction in cardiac output, and a concomitant 30% increase in SVR, although catecholamine concentrations did not change (511). However, the study lacked a control population. These two investigations show that treatment of endogenous SHyper improves cardiovascular parameters, which could be responsible for the increased cardiovascular risk that is present in older SHyper patients. Moreover, treatment of SHyper induced spontaneous reversion of AF to sinus rhythm in four patients (512). This supports the hypothesis that prompt restoration of euthyroidism might induce spontaneous reversion or facilitate cardioversion of AF to sinus rhythm (512). However, no long-term prospective controlled trials have been conducted to see whether chronic treatment to normalize serum TSH levels or treatment with beta-blockers could reduce the risk of AF and other adverse cardiovascular events.

4. Effects of treatment on BMD. Treatment of benign (469, 487) and malignant thyroid disease (468, 497) with L-T_4 doses that induce mild TSH suppression did not significantly affect BMD and was not associated with a risk for osteoporosis in pre- and postmenopausal patients. Moreover, in postmenopausal women with exogenous SHyper, bone turnover was related to the serum TSH level, and a reduction of L-T_4 dose reduced bone turnover, thereby increasing BMD (497).

Calcium supplementation was able to prevent bone loss in postmenopausal patients with exogenous SHyper with inadequate calcium intake (497). A similar effect was obtained in a study of estrogen replacement therapy in which 196 women taking thyroid hormone for a mean of 20.4 yr were compared with 795 women not using thyroid hormone (485). Although TSH values were not reported in this study, it showed that women taking both estrogen and thyroid hormone at a dose of 1.6 μg/kg or greater had a significantly higher BMD than women taking the same L-T_4 dosage alone (485). Furthermore, the BMD of women taking estrogen and T_4 was comparable to the BMD observed in women taking only estrogen. These results show that estrogens can prevent the bone loss induced by suppressive doses of L-T_4 in postmenopausal women. This would be beneficial for postmenopausal women with high-risk DTC who have no contraindications to estrogen replacement therapy. Finally, pamidronate, a bisphosphonate, was able to prevent the increased bone turnover caused by thyroid hormone (490).

Successful treatment of overt hyperthyroidism produces a significant increase in BMD (513, 514). Few studies have evaluated BMD in endogenous SHyper after normalization of serum TSH by radioiodine treatment or antithyroid drugs (501, 502). In one study, 16 postmenopausal women with SHyper due to multinodular goiter underwent radioiodine treatment because of compressive symptoms, whereas 12 asymptomatic postmenopausal women with SHyper remained untreated. After 2 yr of follow-up, BMD remained stable in the spine in the treated group, whereas progressive bone loss occurred in the untreated group. In another study, BMD in the hip increased significantly after 2 yr in the treated group but decreased in the untreated group (501). Similarly, postmenopausal women with SHyper were prospectively monitored for 2 yr. Eight patients were treated with methimazole to achieve euthyroidism and eight remained untreated. At the end of follow-up, distal forearm BMD was stable and significantly increased in the treated group compared with the untreated group (502). However, in a small randomized study of premenopausal women, BMD at baseline was slightly but not significantly different from age-matched controls and did not improve after 6 months of euthyroidism (515).

In conclusion, randomized prospective trials of large groups of patients are necessary to clarify the possible beneficial effects of treatment with antithyroid drugs or radioiodine on BMD in young and middle-aged patients with endogenous SHyper. The available data support the concept that treatment of postmenopausal women with SHyper will be of benefit in terms of improved skeletal health.

K. Treatment guidelines

1. Optimal TSH target for benign and malignant thyroid disorders. Of course, there is no reason to suppress TSH in patients with hypothyroidism who need replacement therapy; the goal of treatment is to maintain TSH in the normal range, and thyroid function should be periodically assessed to avoid under- or overtreatment.

TSH suppressive therapy in the management of patients with nontoxic solid thyroid nodules is a controversial issue in terms of efficacy, the optimal level of TSH suppression, the optimal duration of treatment, and potential side effects (516). This treatment has been used for over half a century to shrink nodules, to prevent growth of nodule (s), and to prevent the appearance of new nodules. Complete regression of thyroid nodules is unusual. In a prospective multicenter, randomized, double-blind, placebo-controlled French trial, L-T_4 suppressive therapy reduced the growth of solitary thyroid nodules and prevented the development of new nodules (517). In another study, L-T_4 therapy (to suppress serum TSH to below 0.1 mIU/liter) was able to prevent the development of new lesions and an increase nodule and thyroid size (518). These data might be relevant to populations living in areas of relative iodine deficiency.

Recent guidelines do not recommend routine suppressive therapy with L-T_4 of benign thyroid nodules (363, 519). However, this treatment is still preferred by nearly half the membership of the ATA and the European Thyroid Association, especially in areas of borderline-low iodine intake (520, 521). L-T_4 therapy is less frequently used by members of the Latin American Thyroid Society than by ATA and European Thyroid Association members (522).

Long-term suppressive therapy with serum TSH concentrations below 0.1 mIU/liter is recommended for DTC patients with persistent disease and a high risk of recurrence (362, 363). Beta-blockade might be considered in high-risk thyroid cancer patients with adrenergic hyperresponsiveness to L-T_4 (4, 362). In the case of long-term serum TSH suppression, supplemental calcium and bone-sparing drugs should be considered, especially in postmenopausal women to reduce the risk of osteoporosis and possibly fractures. In low-risk patients with no evidence of disease (patients with undetectable suppressed and stimulated serum thyroglobulin and negative ultrasound of the neck after thyroidectomy and radioiodine ablation), the long-term risk of recurrence is less than 1%, and the goal of L-T_4 treatment should be to maintain the TSH level in the lower limit of the normal range. Clinicians should prescribe the lowest possible dose of L-T_4 to achieve the desired TSH concentration in patients with benign and malignant thyroid disease.

2. Treatment of endogenous SHyper. Opinions differ about the treatment of endogenous SHyper (338, 523). According to the American College of Physicians' guidelines, the potential benefits of treating patients with SHyper are only theoretical, and the management of patients without clinical findings is not clear (338). A recent panel of experts recommended against routine treatment for those patients whose TSH is mildly decreased; treatment was recommended for those with serum TSH levels below 0.1 mIU/liter who were older than 60 yr; for those with or at increased risk of heart disease, osteopenia, or osteoporosis; or those with symptoms of hyperthyroidism (6). Individual assessment for treatment or follow-up is recommended for younger individuals with SHyper and serum TSH persistently below 0.1 mIU/liter. The same opinion was expressed by the American Association of Clinical Endocrinologists, the ATA, and The Endocrine Society (5). A case-based mail survey of ATA members on the management of patients with SHyper showed that most recommended observation alone for young patients with a low but detectable serum TSH (84%) or an undetectable TSH (58%) (524). However, 66% favored treating older patients who had an undetectable serum TSH. Radioactive iodine was considered the treatment of choice for toxic multinodular goiter.

Although it has not been demonstrated that early treatment of symptomatic patients with SHyper improves clinical outcome, treatment of SHyper might improve quality of life, cardiovascular risk factors, and BMD, and would prevent a possible progression to overt disease. Before treatment is started, it should be established whether the subnormal serum TSH is related to endogenous SHyper and whether it is persistent (Fig. 5). In the presence of low or undetectable serum TSH and normal free thyroid hormones, other causes of transient TSH suppression (thyroiditis, nonthyroidal illness, pregnancy, or medications) should be excluded. A 24-h radioiodine uptake and thyroid scan should be considered to establish the correct etiology of the disease and the possible therapeutic approach. Neck ultrasound is used, especially in areas of iodine deficiency, to identify the nodules for fine-needle biopsy before definitive treatment with radioiodine. Thyroid function should be reevaluated after 2, 4, and 6 months in asymptomatic patients with suppressed serum TSH to establish whether SHyper is a persistent or progressive disease. If serum TSH remains suppressed, therapy will depend on the results of clinical assessment of the possible risk factors related to the disease (Fig. 5).

Young, asymptomatic patients with low but detectable TSH should undergo periodic follow-up without treatment. In young and middle-aged symptomatic patients, especially those with undetectable serum TSH, palpitations, or a history suggesting atrial arrhythmias, the cardiac effects should be assessed to establish the cardiovascular risk. In this case, ECG and ambulatory Holter ECG can be used to evaluate the presence of atrial arrhythmias, whereas Doppler echocardiography can be used to assess the presence of left ventricular hypertrophy, possible alterations of cardiac function, and possible underlying structural heart disease. Symptomatic young patients with undetectable serum TSH should be treated with antithyroid drugs to normalize serum TSH. Treatment with antithyroid drugs for 3–6 months can be used to evaluate the possible beneficial effect of TSH normalization on quality of life, heart rate, and atrial premature beats before definitive treatment with radioiodine or surgery. Low doses of antithyroid drugs (methimazole 5–15 mg/d, or propylthiouracil 50–150 mg/d) are usually able to normalize serum TSH in SHyper. As an alternative, beta-blocking drugs should be considered. However, definitive treatment of SHyper should be considered in symptomatic patients with endogenous SHyper in the presence of underlying heart disease, AF, or left ventricular hypertrophy.

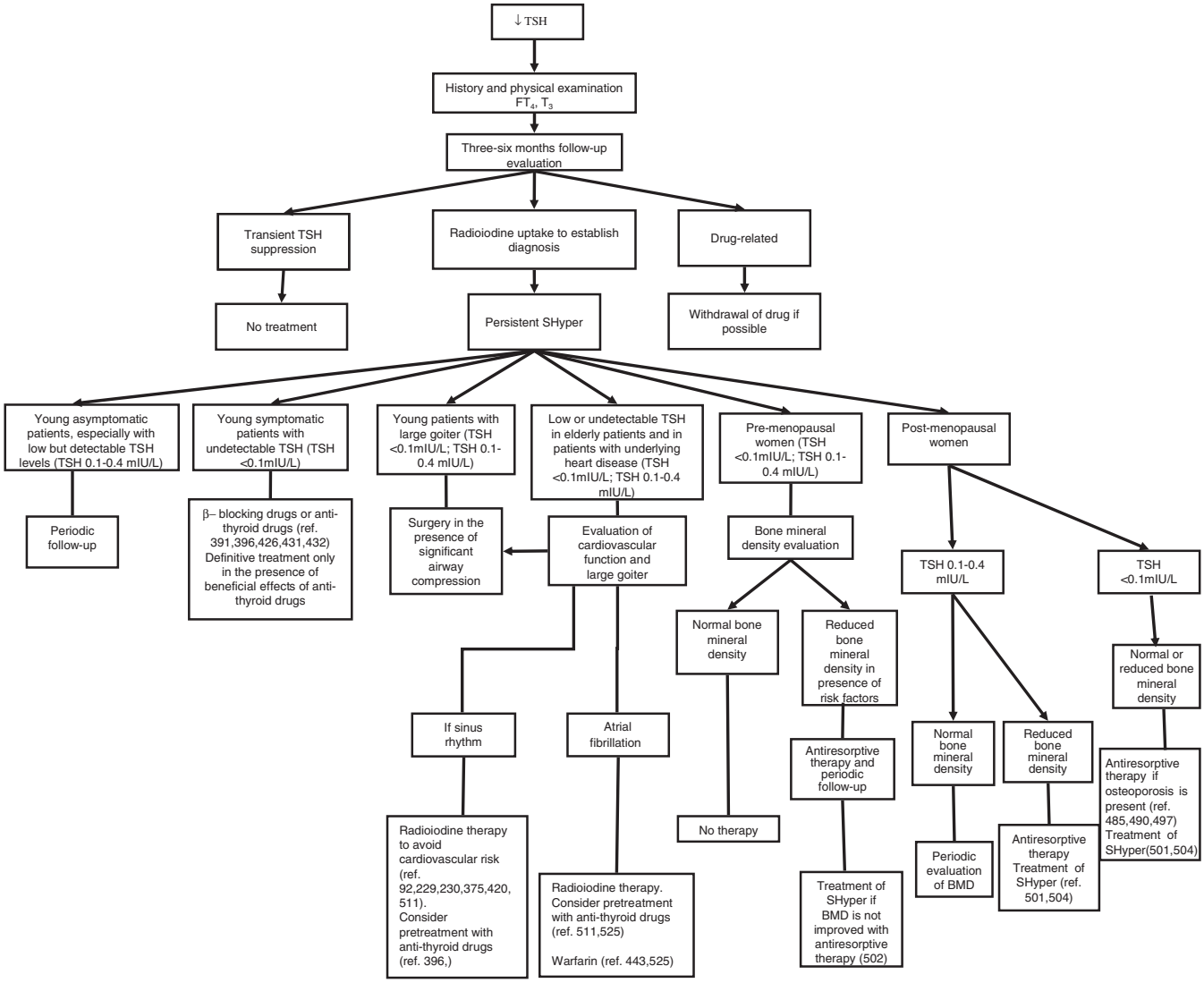

FIG. 5. Algorithm for the diagnosis and treatment of SHyper.

In elderly or postmenopausal patients, definitive treatment of SHyper in the presence of low or undetectable serum TSH should be considered because of the increased risk of AF and the risk of osteoporosis in this age group. In older patients with or without AF, ablative therapy with ^{131}I is the preferred option for most patients. However, in patients with AF or underlying heart disease, antithyroid drug therapy should be considered to reverse AF and to improve cardiac function. Furthermore, it is prudent to restore normal thyroid function before radioiodine in such patients to avoid a possible worsening of thyroid function after therapy. Treatment of thyrotoxicosis with antithyroid drugs can cause spontaneous reversion of AF to sinus rhythm in two thirds of patients with overt hyperthyroidism within 8–10 wk (525). β-Adrenergic blockade may be useful to control ventricular rate, and anticoagulation should be considered.

Only two studies, which both involved small numbers of patients with SHyper, reported conversion of AF to stable sinus rhythm after treatment with radioiodine or antithyroid drugs (381, 512). There are no controlled studies comparing the efficacy of different therapies (antithyroid drugs, radioiodine, or surgery) in patients with SHyper. The options for definitive therapy are based on the considerations recommended for overt disease (364, 526).

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Erratum

In the article "Uteroglobin: A Steroid-Inducible Immunomodulatory Protein That Founded the *Secretoglobin* Superfamily" by Anil B. Mukherjee, Zhongjian Zhang, and Beverly S. Chilton (*Endocrine Reviews* 2007, 28:707–725), Fig. 3 was printed with missing text. The corrected figure and the legend appear below.

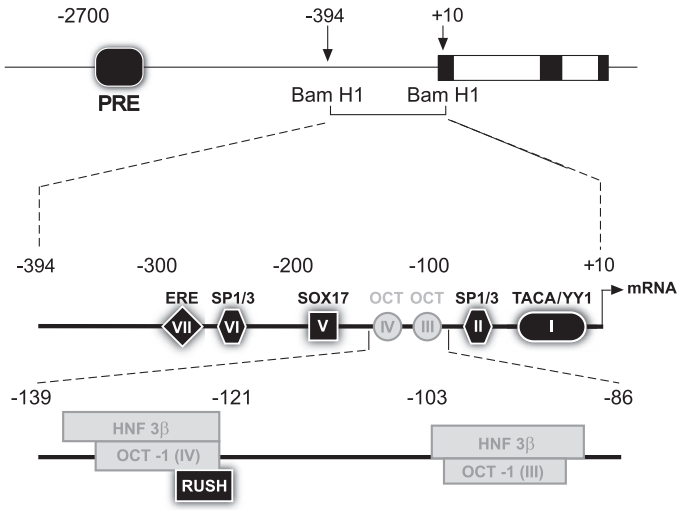

FIG. 3. Organization of the UG gene. The three exons are *black boxes*, and the intervening introns are *open boxes*. PRE designates a cluster of progesterone response elements. The 404-bp *Bam*H1 rabbit promoter (−394/+10) is enlarged to show the locations of an ERE, two Sp1/3 binding sites, a SOX17 site, a RUSH (RUSH/SMARCA3) site, and a YY1 site juxtaposed to the TACA box. The cis-binding sites that are most important in the rabbit promoter are shown in *bold* relief against less important elements.