Endocrine, *vol. 24, no. 1, 1–13, June 2004* 0969–711X/04/24:1–13/$25.00

CLINICAL UPDATE

Hypothyroidism as a Risk Factor for Cardiovascular Disease

Bernadette Biondi[1] and Irwin Klein[2]

[1]Department of Clinical and Molecular Endocrinology and Oncology, University of Naples Federico II School of Medicine, Via S. Pansini 5, 80131, Naples, Italy and [2]Division of Endocrinology and Department of Medicine, North Shore University Hospital and Department of Cell Biology, NYU School of Medicine, New York, NY

The cardiovascular risk in patients with hypothyroidism is related to an increased risk of functional cardiovascular abnormalities and to an increased risk of atherosclerosis. The pattern of cardiovascular abnormalities is similar in subclinical and overt hypothyroidism, suggesting that a lesser degree of thyroid hormone deficiency may also affect the cardiovascular system. Hypothyroid patients, even those with subclinical hypothyroidism, have impaired endothelial function, normal/depressed systolic function, left ventricular diastolic dysfunction at rest, and systolic and diastolic dysfunction on effort, which may result in poor physical exercise capacity. There is also a tendency to increase diastolic blood pressure as a result of increased systemic vascular resistance. All these abnormalities regress with L-T_4 replacement therapy. An increased risk for atherosclerosis is supported by autopsy and epidemiological studies in patients with thyroid hormone deficiency. The "traditional" risk factors are hypertension in conjunction with an atherogenic lipid profile; the latter is more often observed in patients with TSH >10 mU/L. More recently, C-reactive protein, homocysteine, increased arterial stiffness, endothelial dysfunction, and altered coagulation parameters have been recognized as risk factors for atherosclerosis in patients with thyroid hormone deficiency. This constellation of reversible cardiovascular abnormalities in patient with TSH levels <10 mU/L indicate that the benefits of treatment of mild thyroid failure with appropriate doses of L-thyroxine outweigh the risk.

Key Words: Subclinical hypothyroidism; mild thyroid failure; atherosclerosis; hypertension; endothelial dysfunction; homocysteine; C-reactive protein; lipid metabolism; heart failure.

Received March 15, 2004; Revised April 21, 2004; Accepted April 26, 2004.

Author to whom all correspondence and reprint requests should be addressed: Dr. Irwin Klein, Division of Endocrinology, North Shore University Hospital, Manhasset, NY 11030. E-mail: iklein@nshs.edu

Introduction

Hypothyroidism is characterized by decreased thyroid hormone production by the thyroid gland. This in turn leads to decreased hormone levels in cells and tissues *(1–3)*. It ranges in severity from a mild subclinical form to overt hypothyroidism and myxedema. Subclinical hypothyroidism (sHT) has long been viewed as a compensated peripheral thyroid condition in which serum thyroid hormone concentrations (free T_4 and free T_3) are within the laboratory reference range, and the increase in thyroid-stimulating hormone (TSH) simply reflects the pituitary adaptation to maintain these levels. However, mounting evidence supports the notion that the elevated TSH of sHT reflects an early and mild form of thyroid failure associated with demonstrable signs of tissue hypothyroidism *(1–7)*.

The cardiovascular system is one of the major targets of thyroid hormone action, and is a reliable marker of peripheral thyroid hormone action *(1,4–7)*. It is sensitive enough to detect the effects of thyroid hormone deficiency at tissue level not only in patients with overt but also in individuals with mild thyroid failure *(1,5–7)*. The pituitary gland is very sensitive to variations in thyroid hormone concentrations because it derives triiodothyronine (T_3) from deiodination of thyroxine (T_4) by way of type II 5' monodeiodinase. Type II 5' monodeiodinase RNA has also been found in heart (primarily in the non-muscle heart cells) and vascular smooth muscle (VSM) cells of the aorta and coronary arteries *(8)*. This suggests that type II 5' monodeiodinase may also play a role in the aorta and coronary arteries, and, consequently, that the cardiovascular system may respond physiologically as does the pituitary gland to fluctuations in the serum levels of thyroid hormone levels.

Thyroid hormone affects the heart and vascular system by classic genomic as well as by non-genomic mechanisms *(7,9)* (Fig. 1). The well-characterized mechanism of thyroid hormone action is mediated via T_3 binding to the nuclear receptors to induce the transcription of genes that encode specific structural and regulatory proteins in many cell types including cardiomyocytes and VSM cells *(7)*. The thyroid hormone response to structural and regulatory proteins in the heart is well known *(1,7)* (Table 1). Moreover, thyroid

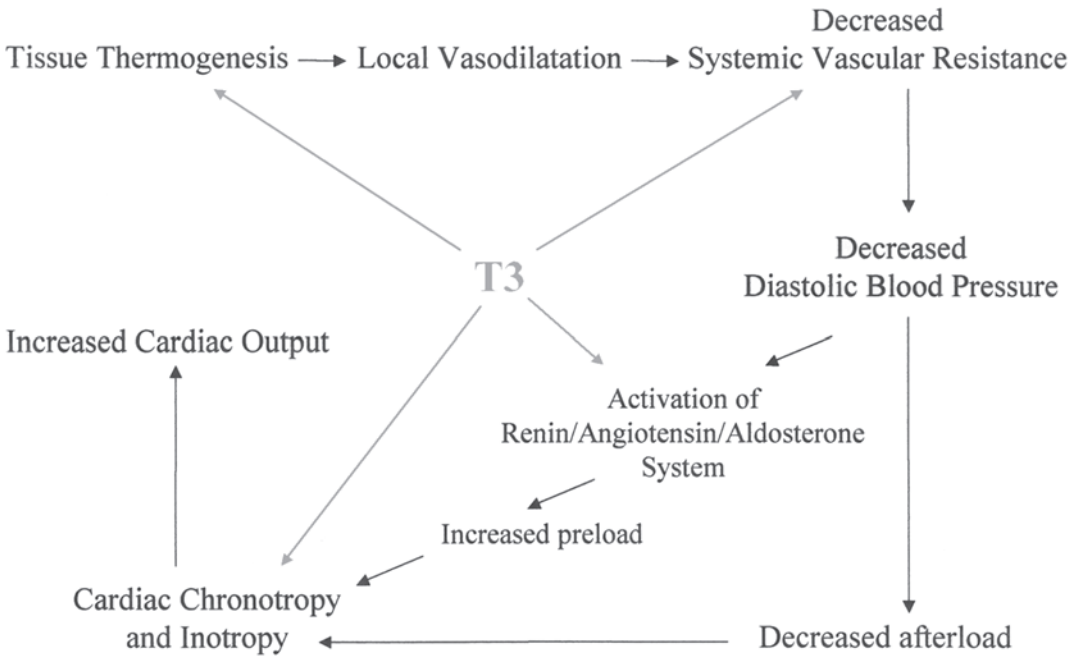

Fig. 1. Sites of thyroid hormone action on the systemic vasculature and the heart.

Table 1
Thyroid Hormone Response Myocyte Proteins

Positive regulation	Negative regulation
α-myosin heavy chain	β-myosin heavy chain
Sarcoplasmic reticulum Ca^{2+}-ATPase	Phospholamban
β_1-adrenergic receptors	Adenylyl cyclase types V and VI
Guanine-nucleotide-regulatory proteins	Triiodothyronine nuclear receptor α1
Na^+/K^+ -ATPase	Na^+/Ca^{2+} exchanger
Voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3)	

hormone can directly and nongenomically interfere with ion channels in cardiomyocytes that are responsible for the acute alteration of cardiovascular parameters *(9)*.

Causes, Prevalence, and Progression of Thyroid Hormone Deficiency

The causes of sHT and overt hypothyroidism (oHT) are the same *(10)*. Most patients have chronic autoimmune thyroiditis with positive tests for serum antithyroid peroxidase (anti-TPO) antibodies. The incidence of hypothyroidism is about 70–90% after radioiodine therapy or thyroid surgery *(10)*. External irradiation of the neck can cause hypothyroidism with a dose-dependent effect. Central hypothyroidism is rare. It may be caused by tumors involving the hypothalamus, the suprasellar region, or the pituitary gland, or by surgery or radiotherapy of these tumors. Iodine excess can also cause hypothyroidism by inhibiting iodine organification and thyroid hormone synthesis. Drugs may induce sHT or oHT; cases in point are lithium carbonate and iodine-containing medications such as amiodarone, radiographic contrast agents, cough medicines, and dietary supplements *(10)*. Interferon-alpha can cause hypothyroidism by inducing thyroid autoimmunity. In addition, patients with hypothyroidism who are taking levo-thyroxine (L-T_4) may become hypothyroid if given drugs such as cholestiramine or iron salts that decrease T_4 absorption, or drugs such as carbamazepin that increase T_4 clearance. Poor compliance to L-T_4 therapy or suboptimal treatment may also result in sHT. Therefore, the diagnosis of sHT or oHT can be made only after controlling for drugs or substances that may interfere with thyroid gland function or with the laboratory assay *(11)*.

It can be difficult to distinguish between transient disturbances of thyroid gland function and mild unrecognized

thyroid failure. Transient increases in TSH may be due to destructive thyroiditis (post-partum or subacute thyroiditis). Concentrations of TSH may also be increased after recovery from severe illness, especially in the elderly and in cases of adrenal insufficiency. A high thyroid autoantibody titer and a high serum TSH concentration strongly indicate ongoing thyroid gland disease.

In the recent National Health and Nutrition Examination Survey (NHANES III) survey of 17,353 Americans, the prevalence of sHT and oHT was, respectively, 0.3 and 4.3% and was higher in Caucasians than in Hispanics and Blacks *(12)*. There is a high prevalence of sHT and oHT in the elderly. The largest survey to report age- and gender-specific prevalence data on sHT is the Colorado Study *(13)*. In this survey of more than 25,000 people, the prevalence of elevated TSH was 9.5%, and the prevalence of mild hypothyroidism (mHT), defined as TSH greater than 5.1 mU/L in individuals not taking T_4, was approx 4% in individuals aged between 18 and 24, and it rose to 16% in elderly men and to 22% in elderly women. The prevalence of sHT among patients taking thyroid replacement therapy was 17.6%.

If not treated, sHT can progress to oHT. In the 20-yr follow-up of the Wickham cohort study, the hazard rate (the estimate of the probability of developing hypothyroidism at a particular time) increased with age to 13.7% in women between 75 and 80 yr of age *(14)*. Serum TSH concentration above 2 mU/L was associated with an increased probability of developing oHT, and the probability was further increased in individuals with antithyroid antibodies *(14)*. About 2% to 5% of sHT patients a year will progress to overt disease.

Given the high prevalence of sHT and oHT in the general population and particularly in the elderly, it is important to establish whether these alterations of thyroid function entail a cardiovascular risk in order to form the basis for rational testing and therapy *(2,3,5,10)*.

Cardiovascular Risk in Patients with Hypothyroidism

As shown in Table 2, the cardiovascular risk in patients with thyroid hormone deficiency results from the changes in cardiovascular hemodynamics, alterations in cardiac phenotype and contractility, and accelerated atherosclerosis. Thyroid hormone affects the cardiovascular system in various ways *(4–7,15–18)*. T_3 influences heart rate, systolic function, diastolic function, and systemic vascular resistance producing the classic effects on cardiovascular hemodynamics *(4,7)*. The first report of hypothyroid heart was reported by Zondek in 1918. He described the enlarged cardiac silhouette caused by pericardial effusion, present in at least 30% of cases of untreated and long-standing hypothyroidism *(19)*. Myofibrillar swelling interstitial edema and interstitial fibrosis have been found on histological examination of cardiac tissue from autopsy specimens of patients dying with severe hypothyroidism *(20)*.

Table 2
Thyroid Hormone Deficiency and Cardiovascular Risk

Increased risk for functional cardiovascular changes
• Normal/depressed systolic function at rest
• Left ventricular diastolic dysfunction at rest and during exercise
• Impaired left ventricular systolic function on exercise
• Increased systemic vascular resistance
• Increased prevalence of diastolic heart failure in the elderly
Increased risk for atherosclerosis
• Increased prevalence of hypertension
• Altered flow-mediated endothelium-dependent vasodilatation
• Atherogenic lipid profile
• Hyperhomocysteinemia
• Coagulation abnormalities
• Elevated C-reactive protein levels

Cardiac output is decreased in severe hypothyroidism as a result of a decrease in both stroke volume and heart rate *(6,7,21,22)*. Stroke volume is determined by the interaction between myocardial contractility, preload and afterload. In early studies, the decreased cardiac output observed in hypothyroid patients was attributed to abnormalities of myocardial contractility. The effect of thyroid hormone on myocardial contractility is well documented in animals and humans *(21–26)*. Thyroid hormone induces transcription of the alpha-myosin heavy chain gene and the sarcoplasmic reticulum calcium activated ATPase (SERCA2), while it represses expression of the beta-myosin heavy chain gene and phospholamban *(27)*. Recent studies demonstrate that the cardiac phenotype is exquisitely sensitive to dynamic changes in serum T_3 *(11)*. In humans, changes in myocardial gene expression were documented by measuring mRNA extracted from endomyocardial biopsy specimens of a hypothyroid patient with dilated cardiomyopathy, before and after thyroxine replacement therapy *(28)*. In this patient, the administration of thyroid hormone produced an increase of alpha-myosin heavy chain gene expression with a trend toward the beta-to-alpha myosin heavy chain shift. In human ventricle, however, the beta isoform of the myosin heavy chain is more prevalent than the alpha isoform, and their ratio is probably only marginally modified by thyroid hormone *(29)*. The T_3-induced changes in the expression of myosin heavy chain isoforms are probably too slight to account for the functional alterations of the heart in hypothyroidism. There are changes in myosin heavy chain isoform expression in the human atria in congestive heart failure, and it remains to be determined whether these changes are thyroid hormone–mediated *(30)*.

There is evidence that thyroid hormone directly affects cardiac contractility, both systolic and diastolic function, by regulating calcium cycling through the sarcoplasmic reticulum Ca-ATPase (SERCA)–phosholamban system *(31–33)*.

Triiodothyronine stimulates SERCA2 transcription while simultaneously repressing phospholamban expression. The latter protein exerts an inhibitory effect on SERCA2-mediated calcium cycling and thus the effect of thyroid hormone on these two proteins is synergistic *(31)*. The rate of calcium release and its reuptake into the sarcoplasmic reticulum are important determinants of systolic contractility and diastolic relaxation. Thus, regulation of the amounts of these proteins in the myocyte explain the observed effects of T_3 on myocardial contractility *(34)*. Transgenic animal studies further support this conclusion *(35)*.

In 1967 Buccino et al. examined the effects of thyroid hormone on the cat isolated papillary muscle *(24)*. Both shortening velocity and tension development were significantly decreased in the muscle from hypothyroid cats compared with the muscle from euthyroid animals; this finding was confirmed in intact dogs *(23)*. In humans, decreased contractility was documented by an invasive technique in myxedema *(21)*. However, both decreased *(36)* and unaltered *(37–39)* systolic cardiac function have been reported in noninvasive studies of at-rest myocardial contractility in patients with hypothyroidism. Recent data support the hypothesis that decreased cardiac output in hypothyroid patients at rest depends largely on changes in diastolic relaxation and hemodynamic loading conditions *(6,7,34)*.

Preload is largely determined by total blood volume and venous return as well as by the contractile activity of the atrium and the filling property of the ventricle. Preload is reduced in hypothyroid patients, which coincides with the finding that blood volume is decreased in hypothyroidism *(40,41)*. Moreover, a decreased rate of active diastolic function is detectable at a very early stage of hypothyroidism. This is supported by the observation that it is present in mHT and in short-term hypothyroidism *(42,43)*.

Prolonged isovolumic relaxation time of the left ventricle was first reported in 1976 *(44)*. This index of relaxation of the cardiac muscle, identified by means of combined apex cardiography and phonocardiography, returned to normal after thyroxine replacement therapy *(44)*. Simultaneous electrocardiography, phonography, apex cardiography, and echocardiography revealed that isovolumic relaxation time was significantly longer in hypothyroid patients than in control subjects, which is indicative of impaired passive relaxation of the left ventricle *(37)*. This condition was completely reversed after 3 mo of thyroxine replacement *(37)*. Impaired left ventricular diastolic function, characterized by slowed myocardial relaxation and impaired early ventricular filling, has been confirmed in hypothyroid patients by means of radionuclide ventriculography and Doppler echocardiography *(39,45,46)*. Diastolic function assessed by pulsed Doppler echocardiography improved after replacement therapy *(45,47)*.

Asymmetric septal hypertrophy has been observed in hypothyroid patients and in some instances it was reverted by the euthyroid state *(48)*. This condition may be another cause of left ventricular diastolic dysfunction, or it might simply reflect an adaptive response to the increased afterload, especially in the elderly *(49)*.

The peripheral circulation in hypothyroidism is characterized by increased vascular resistance and a prolonged circulation time *(7)*. This results in a redistribution of blood flow and a fall in renal flow. Plasma renin and aldosterone levels are decreased in hypothyroidism, which suggests that the renin–angiotensin–aldosterone system plays a minor role if any in hypothyroidism-induced hypertension *(50)*. Because plasma volume is decreased in hypothyroidism, the main contributor to hypertension is the increased peripheral vascular resistance. The increased cardiac afterload can further reduce cardiac output, thereby contributing to the prolonged circulation time observed in hypothyroidism. Afterload is increased in patients with hypothyroidism as a result of increased systemic vascular resistance and arterial stiffness, and is one of the major factors determining myocardial oxygen consumption *(7,51–53)*. The increase in afterload can account for the finding that the hypothyroid myocardium is energy-inefficient notwithstanding the low level of overall oxygen consumption *(54)*.

The earliest response to acute thyroid hormone administration in animals and humans is a fall in systemic vascular resistance *(55–57)*. The T_3-induced decrease in systemic vascular resistance may be explained by direct modulation of endothelium-dependent and -independent vasoregulation *(55–60)*. Triiodothyronine directly affects the vascular smooth-muscle cells (VSMC) that promote relaxation; it also decreases systemic vascular resistance by increasing tissue thermogenesis and metabolism *(7)*. Recent data documenting deiodinase type II expression in cultures of human coronary artery smooth-muscle cells and of human aortic smooth-muscle cells suggest that T_3 locally produced from T_4 could contribute to the regulation of vascular tone in normal and pathophysiological conditions *(8,60)*. The vascular endothelium is a regulator of VSMC and helps to maintain homeostasis and blood fluidity; nitric oxide (NO) in the endothelium diffuses to the vascular smooth muscle and induces relaxation. Hypothyroidism and sHT have been associated with a reversible state of endothelial dysfunction and reduced NO availability *(61,62)*.

It has long been known that chronic hypothyroid patients have increased peripheral arterial resistance *(21,63)*. Moreover, as early as 1931, an elevation of diastolic blood pressure was found to be common in patients with hypothyroidism, and it decreased when euthyroidism was reached *(64, 65)*. In the presence of hypothyroidism, systemic arterial hypertension increases by as much as 30%, mean arterial pressure rises, and 20% of patients have diastolic hypertension *(7)*. Menof was the first to report that thyroid hormone had a beneficial effect on blood pressure *(66)*. He found that desiccated thyroid administration lowered blood pres-

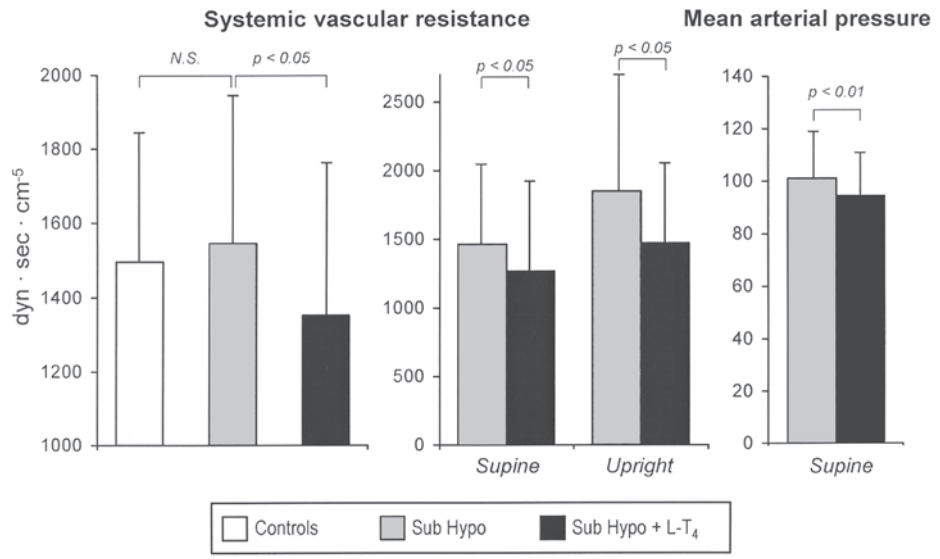

Fig. 2. Systemic vascular resistance and mean arterial pressure in two studies of subclinical hypothyroid patients before and after levothyroxine therapy.

sure to normal level in 14% of 334 patients with essential hypertension. The effect on systemic vascular resistance of thyroid hormone deficiency is an early alteration being documented in both short-term and sHT *(67–69)*.

The endothelial dysfunction that is present in hypothyroid patients may predispose to atherosclerosis and increased arterial stiffness. The increased central arterial stiffness may further contribute to the development of hypertension in hypothyroidism *(51,52)*. Aortic stiffness and systemic vascular resistance are increased in all patients with hypothyroidism whether or not they have hypertension; the effects of the two disorders are additive *(51)*. Aortic stiffness and systemic vascular resistance may decrease during T_4 therapy in hypothyroid patients with normal blood pressure and in patients with persistent hypertension. However, patients with higher basal values of aortic stiffness are less likely to have normalization of systolic blood pressure, and the decrease in systolic blood pressure is correlated with the decrease in aortic stiffness *(51)*. Impairment of the elastic properties of the aorta may be the cause of the incomplete normalization of blood pressure after replacement therapy in 50% of patients with hypothyroidism and hypertension thereby suggesting the need for adjuvant antihypertensive treatment *(51)*.

In summary, the cardiovascular abnormalities frequently associated with oHT are subnormal left ventricular systolic function, as demonstrated by slightly reduced values of ejection fraction and stroke volume, reduced cardiac preload, depressed left ventricular diastolic relaxation, and remarkably increased afterload with subnormal cardiac output *(6,7)* (Table 2). The lower cardiac performance and the abnormalities in peripheral vascular function may contribute to poor exercise tolerance in oHT *(70)*. The most consistent cardiac abnormality seen in patients with oHT is impaired left ventricular diastolic function, which is characterized by slowed myocardial relaxation and impaired early ventricular filling. The increase of left ventricular mass that may be present in patients with hypothyroidism with coexistent hypertension may further contribute to the impaired left ventricular filling related to the presence of impaired diastolic relaxation. Levo-thyroxine therapy completely reverses these cardiac abnormalities; it improves myocardial contractility, diastolic function and systolic function, and produces a fall in systemic vascular resistance which reduces afterload (Figs. 2 and 3) *(6,7,37,46,47,51,71,72)*.

Hypothyroidism rarely leads to heart failure in the absence of underlying cardiac disease because the decreased cardiac output matches the decreased peripheral metabolic demand *(6,7)*. However, diastolic dysfunction may be particularly hazardous in the elderly, regardless of the presence of underlying cardiovascular disease. Aging is accompanied by the development of cardiac hypertrophy, interstitial fibrosis, and myocyte loss, which may itself be responsible for diastolic dysfunction and reduced cardiovascular performance. In this vulnerable population, hypothyroidism may adversely affect cardiac function and hemodynamic status and lead to diastolic heart failure *(6)* (Fig. 4).

A chronic condition of diastolic heart failure is well recognized in the elderly *(73–75)*. About 40% of elderly subjects with heart failure have preserved normal levels of systolic ejection fraction *(75)*. These patients have been characterized with increased vascular stiffness, increased myocardial fibrosis, and altered myocardial calcium handling *(75)*. Diastolic heart failure is associated with hypothyroidism and conversely mild hypothyroidism is found in

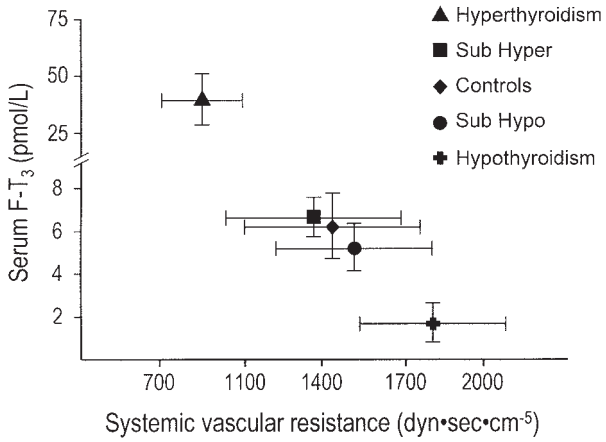

Fig. 3. Correlation between serum T3 levels and systemic vascular resistance in 103 normotensive patients with different degrees of thyroid dysfunction.

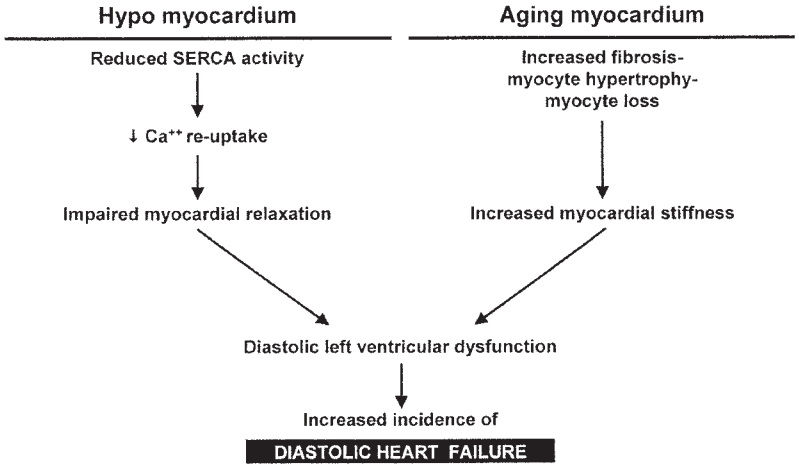

Fig. 4. Thyroid hormone deficiency and the aging myocardium.

patients with chronic heart failure, particularly in elderly women with preserved left ventricular systolic function *(77)*.

Cardiovascular Abnormalities in Patients with Subclinical Hypothyroidism

The impact of sHT on the cardiovascular system has been evaluated by looking at systolic function, diastolic function, exercise performance, and cardiac anatomy *(5,42)*. Systolic contractile function, as assessed by means of systolic intervals, was unchanged in early studies of patients with sHT compared to normal subjects *(72,78–81)*. In contrast, more sensitive echocardiographic studies showed that left ventricular systolic function at rest was impaired, as indicated by a prolonged pre-ejection period and an increased pre-ejection period/left ventricular ejection time ratio in patients versus normal controls *(82,83)*. Moreover, mean aortic acceleration, a reliable index of systolic function, was reduced in patients with sHT compared to controls *(84)*. Diastolic function as measured by the isovolumic relaxation time (IVRT) was prolonged and the ratio of Doppler-derived early and late diastolic transmitral flow velocity was lower in patients with mild thyroid failure with a TSH range between 5 and 10 mU/L than in controls *(83,84)*. These results obtained in young and middle-aged patients affected by Hashimoto's thyroiditis with a mild but stable TSH increase indicate that diastolic dysfunction, as measured by a prolongation of left ventricular relaxation, is a common finding in patients with mild thyroid failure. Diastolic dysfunction at rest and during exercise has also been documented in mild thyroid failure by means of radionuclide ventriculography *(85)*.

Systolic function on effort, evaluated by radionuclide ventriculography, is impaired in sHT patients *(86,87)*. Moreover, impaired cardiac function on effort and reduced physical exercise capacity were documented in sHT patients by stress two-dimensional and Doppler echocardiography combined with cardiopulmonary exercise testing *(88)*. In a study of myocardial regional function in patients with autoimmune

sHT, pulsed tissue Doppler showed that myocardial precontraction time and myocardial relaxation time were prolonged at the level of the posterior septum and the mitral annulus, which confirms that stable mild thyroid failure is associated with both impaired systolic and diastolic function *(83)*.

Ultrasonic myocardial textural analysis has been used to evaluate textural parameters of the septum and posterior wall in sHT patients *(89)*. 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 an altered myocardial composition that may represent early myocardial structural changes *(89)*.

Response to L-Thyroxine Therapy in Subclinical Hypothyroidism

The first study to evaluate the cardiac effect of replacement therapy in sHT was performed in 1981 *(90)*. L-thyroxine therapy reduced the PEP, the PEP/LVET ratio, and the QKd (the interval from the Q wave on the electrocardiogram to the pulse arrival time at the brachial artery). Normalization of serum TSH levels was associated with changes in QKd measurements even in patients with minimally elevated serum TSH *(90)*. Also diastolic function improved in 10 randomly selected patients with mild thyroid failure who were revaluated after 6 mo of L-T_4 therapy *(84)*. Replacement therapy did not induce significant changes in left ventricular morphology *(84)*. L-thyroxine therapy was found to improve systolic and diastolic function in three randomized placebo-controlled trials involving sHT individuals *(82,91, 92)*. The parameters of videodensitometric analysis improved consequent to L-T_4 treatment *(82)*, as did measurements of systolic and diastolic function during exercise *(85,86)*.

Systemic vascular resistance (SVR) has been assessed in two studies of sHT patients before and after L-T_4 therapy. As shown in Fig. 2, although systemic vascular resistance (SVR) was slightly but not significantly higher in sHT normotensive patients than in controls, it significantly decreased when euthyroidism was reached *(84)*. In the other study, L-T_4 replacement therapy resulted in a 13–20% decrease in SVR in the supine and upright position, a 6% reduction in supine mean arterial pressure, and a 14% increase in upright cardiac output *(93)*. There was a significant inverse correlation between serum T_3 levels and SVR values in a cohort of 103 normotensive subjects affected by different degrees of thyroid dysfunction *(94)* (Fig. 3), and a significant positive correlation between serum TSH and SVR in 31 normotensive subjects with thyroid gland failure varying from sHT to oHT *(93)*. Moreover, the mean diastolic blood pressure was higher in 57 middle-aged women with sHT than in 34 age-matched euthyroid controls (82 vs 75 mmHg; $p < 0.01$), and 20% of women with sHT had diastolic hypertension compared with 3.4% of euthyroid women *(69)*. These results support a link between sHT and the hemodynamic changes including SVR, which can lead to hypertension *(16)*.

Thyroid hormone deficiency can affect endothelial function *(16,61,62)*. Using high-resolution ultrasound imaging of the brachial artery, flow-mediated endothelium-dependent vasodilatation was found to be significantly impaired in hypothyroid subjects with TSH between 4.01 and 10 mU/L and greater than 10 mU/L versus a control group *(61)*. Using the perfused forearm technique, the forearm blood flow response to intrabrachial acetylcholine, an endothelium-dependent vasodilator at baseline and during infusion of the NO inhibitor, N^G-monomethyl-L-arginine (L-NMMA), has been evaluated in sHT patients before and after L-T_4 therapy *(62)*. The vasodilating effect of acetylcholine was significantly reduced in sHT patients versus healthy subjects and was not affected by L-MMNA. After 6 mo of stable euthyroidism, there was a significant improvement in acetylcholine-induced vasodilatation and restoration of the inhibitory effect of L-NMMA. These results indicate that L-T_4 treatment improves endothelium-dependent vasodilatation by restoring NO availability *(62)*.

In conclusion, there is clear evidence that sHT patients, even those with mildly elevated TSH levels, have impaired endothelial function, normal/depressed systolic function, left ventricular diastolic dysfunction at rest, and systolic and diastolic dysfunction on effort, which may result in poor physical exercise capacity, increased prevalence of diastolic blood pressure, and increased prevalence of hypertension. All these abnormalities regress with L-T_4 replacement therapy. The pattern of cardiovascular abnormalities is similar in patients with sHT and oHT, suggesting also that a lesser degree of thyroid hormone deficiency may affect the cardiovascular system.

Risk for Atherosclerotic Cardiovascular Disease (ASCVD) in Patients with Hypothyroidism

Clinical and autoptic studies have shown that coronary artery disease occurs frequently and may progress more rapidly in hypothyroid patients *(95–101)* (Table 2). However, epidemiological studies differ widely in estimates of the prevalence of atherosclerosis and the risk for coronary and systemic vascular disease in patients with sHT *(102–111)*. Of the early studies of mild hypothyroidism and coronary artery disease, one found no evidence of a relationship between the two conditions *(102)*, and two did *(103,104)*.

The Wickham survey, an English population-based cohort study of 2779 men and women, was the first large study to evaluate the relationship between thyroid status and cardiovascular outcomes *(105)*. In this study there was no association between sHT and a history of ischemic heart disease or major electrocardiogram changes in either males or females,

but there was a weak association with minor electrocardiogram changes in females in adjusted analyses. Multiple logistic analysis of data from the 20-yr follow-up of the original Wickham survey cohort did not reveal an association between autoimmune thyroid disease, serum lipids, and mortality or development of coronary artery disease *(106)*. However, many patients with sHT at the original survey received thyroid hormone replacement therapy and the analysis did not distinguish between treated and not treated patients. Similarly, the prevalence of atherosclerotic cardiovascular disease was not increased in sHT subjects in a cross-sectional survey of 3410 elderly people in Maryland; a significantly elevated LDL cholesterol concentration was found only in sHT subjects with a TSH concentration above 10 mU/L *(107)*. A case control study of elderly women suggested an association between sHT and peripheral arterial disease *(108)*.

Striking evidence of a higher prevalence of atherosclerotic cardiovascular disease in sHT patients emerges from a large cross-sectional survey of a random sample of 1149 women aged 55 yr or more living in Rotterdam *(109)*. Patients affected by sHT (defined as TSH >4.0 mU/L and a normal free T_4 level) had a significantly increased age-adjusted prevalence of aortic atherosclerosis and myocardial infarction versus controls. The association was even stronger in women with thyroid peroxidase autoantibodies indicating the presence of autoimmune thyroiditis *(105)*. Thyroid autoimmunity itself, however, was not associated with cardiovascular disease, which suggested that the increased atherosclerosis was mediated by T_4 deficiency rather than by immune dysfunction *(16)*. It was found that the attributable risk percentage for sHT associated with myocardial infarction was within the range of that for the major risk factors for coronary artery disease, i.e., hypercholesterolemia, hypertension, smoking, and diabetes mellitus. Moreover, patients with sHT had lower total cholesterol values than controls, but manifested atherosclerotic vascular disease, suggesting that factors other than total cholesterol contribute to the increased risk for atherosclerosis. Although the levels of other lipids such as low-density lipoprotein (LDL) cholesterol, enhanced low-density lipoprotein oxidation, triglyceride level, and lipoprotein (a) may be responsible for the sHT/cardiovascular disease association, these factors were not explicitly determined in the Rotterdam study.

In a cross-sectional study of 280 subjects over 65 yr of age living in a nursing home, there was a significantly higher prevalence of dyslipidemia and coronary artery disease in patients with sHT versus euthyroid controls (56% versus 16%) *(110)*. However, in the recent cross-sectional New Mexico Elderly Health Survey, there was no consistent significant difference in the prevalence of coronary heart disease or in coronary heart disease risk factors in 112 patients with sHT *(111)*.

Hypothyroidism may increase the risk for atherosclerosis by several mechanisms. It increases arterial stiffness and systemic vascular resistance, which in turn enhance blood pressure. Diastolic hypertension in conjunction with dyslipidemia and increased arterial stiffness are well-recognized risk factors for atherosclerosis *(1,6,7,16,112,113)*. Overt hypothyroidism is characterized by hypercholesterolemia, and a marked increase in LDL and apolipoprotein B because of decreased fractional clearance of LDL due to a reduced number of LDL receptors in the liver *(114)*. Hypothyroidism has been associated with a reversible reduction in the activity of cholesterol-ester transfer protein, hepatic endothelial lipase, 7-alpha hydroxylase, and the hepatic LDL receptor *(101,114–117)*. Moreover, hypothyroidism enhances LDL oxidation *(118)*—a process that is reversed by replacement therapy *(118,119)*. Also, levels of lipoprotein(a), a particularly atherogenic LDL variant, are increased in hypothyroid patients, but their response to replacement therapy is unclear *(120–124)*. Moreover, T_3 and HDL are independently inversely related to coronary atherosclerotic lesion growth *(113)*.

Hyperhomocysteinemia is an independent risk factor for occlusive vascular disease, including coronary atherosclerosis *(125)* and may predispose to atherosclerosis by stimulating LDL oxidation, endothelial dysfunction *(126,127)*, and vascular injury of endothelial cells *(126,127)*. Hyperhomocysteinemia has been reported in patients with hypothyroidism *(128–131)*, and was attributed to a reduced glomerular filtration rate, increased creatinine levels, and low concentrations of folate and vitamin B12 *(132)*. Homocysteine levels normalized after thyroid hormone replacement therapy *(128,129)*.

Elevated C-reactive protein levels *(129)* and coagulation abnormalities *(133,134)* are additional risk factors for atherosclerosis present in hypothyroid patients. Endothelial dysfunction is also documented in patients with hypothyroidism *(61)*. Finally, hypothyroidism may exacerbate the cardiovascular risk associated with cigaret smoking and insulin resistance *(135)*.

Subclinical hypothyroidism as a mild degree of thyroid failure may induce atherosclerosis by various means. In various studies it is associated with an atherogenic lipid profile, endothelial dysfunction, and altered coagulation parameters *(13,16,62)*. The very large population-based Colorado thyroid disease prevalence study showed that sHT is associated with an increase, albeit small, in serum LDL cholesterol *(13)*. Bindels and co-workers reported that, after correction for age, an increase of 1 mU/L in serum TSH is associated with a rise in serum total cholesterol of 0.09 mmol/L (3.5 mg/dL) in women and 0.16 mmol/L (6.2 mg/dL) in men *(136)*. In cross-sectional observational surveys it was shown that, compared with euthyroid controls, subjects with sHT have a variable increase in serum levels of total and LDL cholesterol, higher plasma oxidized LDL cholesterol levels, and marginal changes in serum levels of high-density lipoprotein (HDL) cholesterol and lipoprotein(a) *(101,114,137–*

139). The lipid pattern was more deranged in patients with serum TSH levels greater than 10 mU/L and in those who smoked.

Perhaps of more significance is the response of lipid patterns to L-thyroxine therapy in mild thyroid failure. A meta-analysis of studies of the effect of L-T_4 therapy on the lipid profile in sHT showed that serum total cholesterol was reduced by about 0.2 mmol/L (8 mg/dL or 5%) and serum LDL cholesterol by about 0.3 mmol/L (10 mg/dL) after L-T_4 treatment, whereas triglycerides and HDL cholesterol were unaffected *(138)*. Similarly, L-T_4 therapy had no beneficial effect on lipoprotein(a) *(139)*.

Various risk factors for atherosclerosis have been implicated in sHT including hyperhomocysteinemia, elevated C-reactive protein (CRP) concentrations, and altered coagulation parameters. There were no differences in homocysteine levels between individuals with sHT and euthyroid controls in four case-control studies *(69,111,129,140)*, and homocysteine levels were unaffected by treatment of sHT *(130,140)*. CRP levels were significantly higher in sHT and oHT patients compared with controls, but did not decrease with T_4 treatment *(129)*. Both increased and decreased platelet adhesiveness have been reported in hypothyroidism *(133, 134)*. The degree of hypothyroidism may influence coagulation parameters *(133,141,142)*.

Hypothyroidism and Clinical Manifestations of Coronary Artery Disease

Thallium scintigraphy has revealed abnormalities in perfusion suggestive of myocardial ischemia in patients with hypothyroidism; however, these defects appear to resolve with thyroid hormone treatment suggesting that they are either false positive results or that the changes represent reversible coronary dysfunction *(50,143)*. Because hypothyroidism alters a variety of myocyte membrane ion channels, thallium may not be transported normally into the myocardium independent of blood flow. The hypometabolic state associated with hypothyroidism benefits the ischemic myocardium by lowering oxygen demand. However, as assessed by positron emission tomography (PET), the hypothyroid heart is energy inefficient, and this change is reversed by T_4 treatment *(54)*.

In a large retrospective review, new onset angina pectoris and myocardial infarction were reported to occur infrequently (35 cases) among 1503 hypothyroid patients followed for many years after the administration of thyroid hormone *(144)*. The beneficial effects of thyroid hormone replacement to decrease anginal frequency (38%) was more commonly observed than was disease worsening (16%). The administration of thyroid hormone benefits the hypothyroid heart because it improves ventricular arterial coupling by improving myocardial contractility and diastolic function and reducing afterload, which is the major determinant of oxygen consumption *(1)*. This could explain data showing that thyroid hormone therapy improves myocardial efficiency and leads to regression of anginal symptoms in hypothyroid patients *(54)*. Worsening of angina, myocardial infarction, and death can occur when L-thyroxine therapy is started with a full dose in older patients with ischemic heart disease *(144,145)*. In contrast, ventricular arrhythmias may improve or completely resolve after L-T_4 treatment *(7)*.

Thyroid Hormone Treatment of Patients with Overt and Mild/Subclinical Hypothyroidism

Full replacement doses of L-thyroxine can be safely given to young patients with sHT or oHT not affected by cardiac disease. In elderly patients with known or suspected coronary artery disease and in patients with underlying heart disease, replacement therapy should be started at a low dose and gradually increased while monitoring the patient's condition. Resting and exercise electrocardiograms often show ischemic-like ST segment and T wave changes in hypothyroidism, but these alterations are not a useful test for the evaluation of an associated coronary artery disease, and may disappear after replacement therapy *(7,145,146)*.

In patients with ischemic heart disease or in the elderly it is advisable to start L-thyroxine therapy with low doses (12.5–25 μg/d) and increase the dose every 6 to 8 weeks until euthyroidism is reached *(91)*. In case of instable angina, or worsening or appearance of angina during L-T_4 treatment, the physician should assess the patient for atherosclerotic coronary artery disease. If significant occlusive coronary artery disease is present, hypothyroid patients can undergo by-pass procedures or angioplasty because controlled studies have demonstrated that it is safe to perform these procedures before replacement therapy *(147,148)*.

The target of replacement therapy is a TSH between 0.5 and 2.5 mU/L, which avoids the risks of under- or overtreatment *(5,10,149–151)*. The optimal replacement dose should take into account the age of patients and the cause of hypothyroidism. Indeed, the L-thyroxine dosage should be lower in the elderly and higher in patients with oHT, particularly those who have undergone thyroidectomy or prior ^{131}I treatment for Graves' disease, than in patients affected by mild hypothyroidism and varying degrees of autoimmune thyroiditis *(151)*.

The goal of replacement therapy is to restore serum TSH to the reference range. However, the normal TSH range is a matter of controversy *(152,153)*. The upper limits of a conservative standard population range are 4.5–5.5 mU/L. Subclinical hypothyroidism is so common in the general population that conservative laboratory reference ranges derived from apparently healthy subjects could be contaminated by patients with undetected low levels of thyroid autoimmune disease *(154)*. The "healthy" population upon which the conservative TSH upper range of 4.5–5.5 mU/L was based could have included individuals with occult thyroid insufficiency. In fact, subjects with serum TSH in the upper half

of the reference range (2.0–4.0 mU/L) had higher mean serum cholesterol levels than those with normal serum TSH levels *(155)*, and TSH values over 4.0 mU/L were associated with an increased prevalence of atherosclerosis and myocardial infarction *(109)*.

The NHANES III study showed that in the majority (>95%) of rigorously screened normal euthyroid healthy subjects selected from the general population, the upper limit of TSH concentration reference range decreased to between 2.5 and 3 mU/L after exclusion of subjects with a strong family history of thyroid disease, goiter, or thyroid autoantibodies *(12)*. The US National Academy of Clinical Biochemistry (NACB) recommends the use of this revised normal range with an upper limit lowered to 3 or 2.5 *(153)*, whereas a National Institute of Health (NIH) panel concludes that the upper limit of TSH should remain 4.5–5 mU/L *(152)*. This much debated and currently unresolved issue also impacts on studies of patients with subclinical hypothyroidism *(156)*. In fact, the definition of TSH normal range dictates who are patients and who are controls, and what is the TSH level to aim for with replacement therapy in thyroid hormone deficiency. The results of some studies could be inconclusive if TSH was not completely normalized, according to a true TSH range, after replacement L-T_4 therapy *(156)*. Moreover, there is an individual target organ sensitivity to thyroid hormone deficiency *(157)*, also in relation to genetic predisposition to cardiovascular risk depending on the patient's thyroid function set-point *(158,159)*.

A recent consensus conference formulated to guide the treatment of patients with subclinical thyroid disease recommends starting replacement therapy in patients with subclinical hypothyroidism above a TSH concentration of 10 mU /L, mainly in order to prevent the progression to overt hypothyroidism, because of the absence of sufficient data to support the association of subclinical hypothyroidism with adverse clinical outcomes or benefit of treatment *(152)*. However, replacement therapy was found to improve the lipid profile and cardiovascular abnormalities in two reviews of selected studies in patients with TSH higher than10 mU/L *(5,101)*, providing experimental support to treat patients with subclinical hypothyroidism.

As we have reviewed, mild hypothyroidism can negatively affect the cardiovascular system, especially diastolic function, endothelial function and systemic vascular resistance *(61,62,69,82–84,93)* (Table 2). These effects are reversed by L-T_4 therapy *(61,82–85,93)*. On this basis, from a cardiovascular perspective it seems appropriate to normalize serum TSH levels with appropriate doses of T_4. Thus, the decision to treat subclinical hypothyroidism, rather than being based on a cut-off TSH threshold, should depend on the patient's overall assessment. The treatment of subclinical hypothyroidism would diminish the high cardiovascular risk associated with arterial hypertension, cardiac dysfunction, atherosclerosis, dyslipidemia, or diabetes mellitus.

Although it remains to be established if L-T_4 reduces the risk of cardiovascular events or whether it prevents the progression of pre-existing cardiovascular disease, an intriguing, but uncontrolled retrospective observation showed that progression of angiographic coronary artery disease in oHT subjects on L-T_4 is accelerated in patients with elevated serum TSH in the subclinical hypothyroid range compared with those in whom hormone replacement maintained TSH levels within the normal reference range *(95)*.

In deciding upon treatment of subclinical hypothyroidism in the elderly, one should consider the negative effects of mild thyroid failure on left ventricular diastolic function that can predispose to diastolic heart failure, and also the increased risk of atherosclerosis and myocardial infarction reported in the Rotterdam study in subjects with TSH >4 mU/L *(77,109)*. The potential benefits of treatment might outweigh the risk of treatment if caution is exercised. Replacement therapy is undoubtedly safe if correctly started and if the patient is regularly monitored to ensure that the TSH concentration remains within normal limits.

Although a recent report recommends against routine screening for subclinical hypothyroidism *(160)*, population screening could identify affected individuals that have an increased risk for cardiovascular abnormalities, hypercholesterolemia, hypertension, and coronary and peripheral vascular disease. Indeed, screening for hypothyroidism would probably be more cost-effective than other widely accepted preventive medicine strategies designed for cardiovascular risk reduction *(10,161,162)*.

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