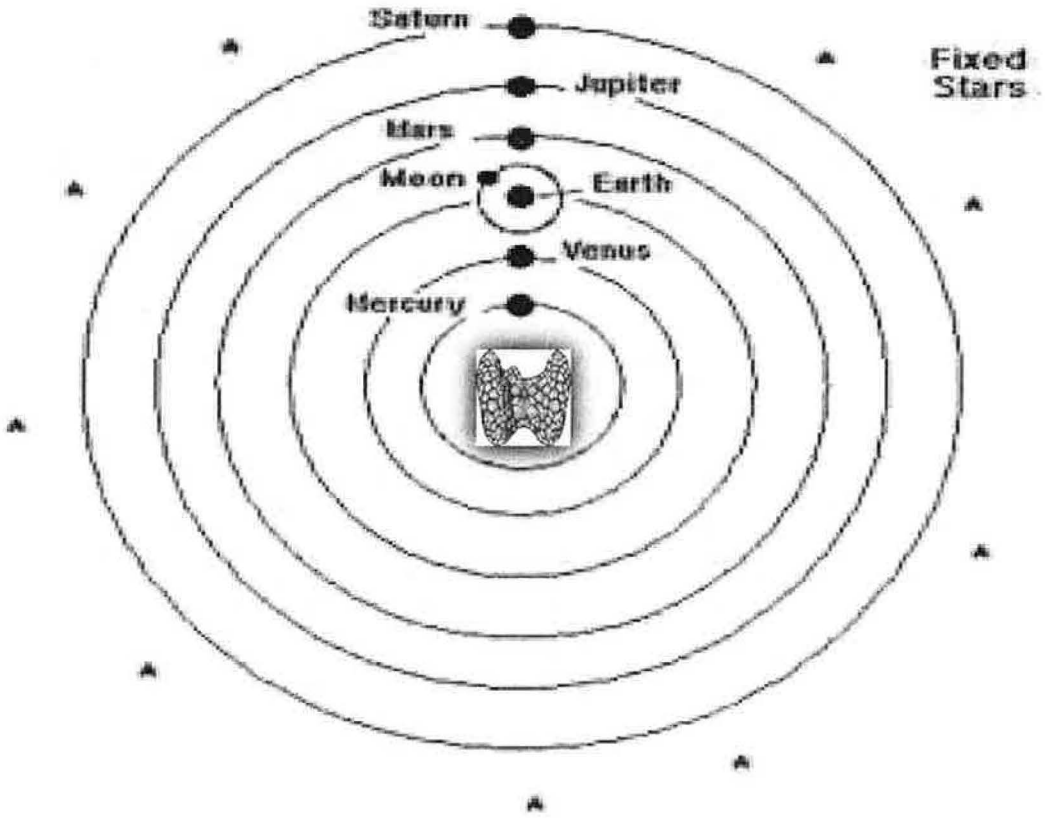
Subclinical Hypothyroidism:

A Thyrocentric View of the Heart



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Biosketch:
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Purpose and Overview:

Subclinical hypothyroidism (SH) is a state of mild thyroid insufficiency that is often seen in asymptomatic, or minimally symptomatic individuals. Laboratory findings include an elevated thyroid stimulating hormone (TSH) with a normal free T4. SH is common with an incidence of 10% in randomly selected populations. Nevertheless, there is controversy regarding the optimal management of SH. This lack of agreement stems from a deficiency in large, randomized prospective trials. As more severe thyroid deficiency is known to have significant cardiovascular consequences, this review looks to the heart to provide insight into the ideal care of these individuals.

Objectives:

- Identify subclinical hypothyroidism as a state of mild thyroid failure with effects on cardiac function and hemodynamics
- Discuss the potential impact of subclinical hypothyroidism on cardiac risk factors and surrogate markers for ischemic cardiovascular disease
- Review impact of levothyroxine therapy on the incidence of cardiovascular events and mortality in subclinically hypothyroid individuals
- Understand the controversy underlying the management of this commonly-encountered clinical scenario

Background:

Hypothyroidism is a frequently encountered clinical entity. Data from the National Health and Nutrition Examination Survey (NHANES III) indicated a total prevalence of abnormal thyroid function of 4.6%. The prevalence increased with female gender, increasing age and was more common in Caucasian versus African-American individuals. (1)

Overt hypothyroidism (OH) is defined as an elevated thyroid stimulating hormone (TSH) accompanied by a reduced serum free thyroxine (fT4) level. These individuals often have the classic symptoms associated with hypothyroidism such as fatigue, weight gain, constipation and cold intolerance. (2)

Subclinical hypothyroidism (SH) is defined as an elevated TSH (> 4 mIU/L) but a normal fT4 level. While patients with SH may have variable symptoms of thyroid dysfunction, others may be asymptomatic. Symptoms, if present, are generally less severe than what is witnessed in patients with OH. (2)

The prevalence of SH is 4-20% of the population. (3) The Colorado Heart Study screened people at statewide health fairs and detected an overall incidence of SH of 11.7%. NHANES III showed an overall rate of 4.3% of the population.(1) Seventy-five percent of people with SH have levels between 5-10 mIU/L. Higher prevalence is associated with increasing age, female gender, and presence of thyroid peroxidase antibodies. SH is also more prevalent among Caucasians than African-Americans. (2)

Despite the fact that SH is commonly encountered in clinical practice, disagreement exists as to the optimal way to manage these individuals.(4, 5) Overt hypothyroidism can result in many adverse effects on the cardiovascular system such as accelerated atherosclerosis, hypertension, hyperlipidemia and rarely, congestive heart failure.(6, 7) The management of OH is unquestionably thyroid hormone replacement; yet for persons with SH, no clear consensus exists as to whether or not to treat when the TSH is elevated but less than 10 mIU/L. The purpose of this discussion is to review what is known about the effect of subclinical hypothyroidism on the cardiovascular system to gain insight into the management of this controversial, yet common scenario.

Physiology of Thyroid Hormone Release:

Thyroid hormone is secreted under the direction of the hypothalamic-pituitary-thyroid axis. The pathway begins in the hypothalamus with the release of thyrotropin-releasing hormone (TRH). TRH flows from the hypothalamus via the hypophyseal-portal capillary system into the anterior pituitary gland where it binds to a TRH-specific receptor found on specialized cells.

Upon binding of TRH to its receptor, the pituitary in turn secretes thyroid stimulating hormone (TSH) into the peripheral circulation. (8)

TSH is a glycoprotein consisting of an alpha and a beta subunit. The alpha subunit is identical to that found in other anterior pituitary hormones, leutinizing hormone (LH) and follicle stimulating hormone (FSH). The beta subunit is specific to TSH and is responsible for the binding of TSH to its receptor on the surface of thyroid follicular cells.

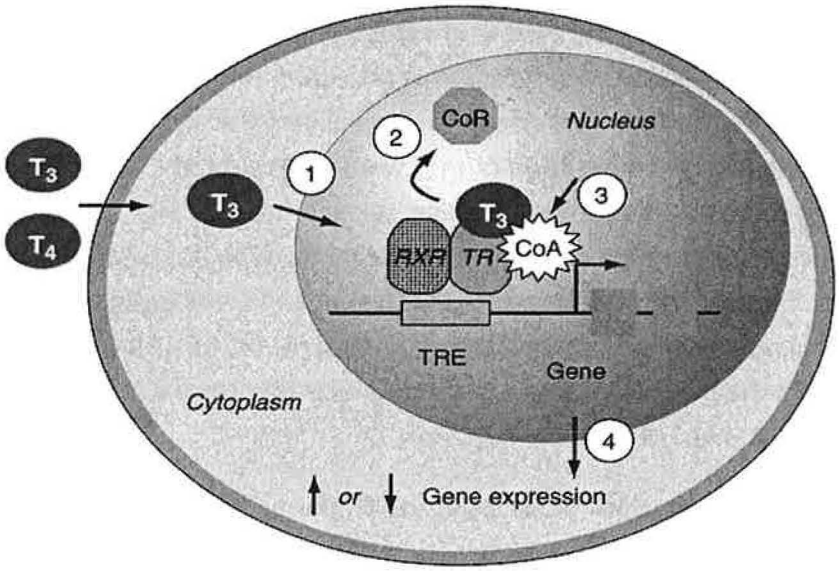
Thyroid hormone circulates in predominately two forms, triiodothyronine (T3) and tetraiodothyronine (T4). Thyroid follicular cells release thyroid hormone in response to binding of TSH to its receptor. About 90% of thyroid hormone released from the thyroid is in the T4 isoform. T3, however, is the more biologically-active isoform and the majority is produced outside of the thyroid gland by way of the 5' mono-deiodinase enzyme system from circulating T4.(8)

Several isoforms of the 5' monodeiodinase enzyme are present. Most tissues (including the liver and kidney) convert T4 to T3 by way of the type 1 isoform (D1). The hypothalamus and pituitary, however, use the type 2 isoform (D2). D2 has a lower Km than D1 and its activity is increased in the setting of hypothyroidism.(9) This enables the pituitary to be extremely sensitive to circulating levels of T4. D2 expression has also been observed in cultured human cardiac smooth muscle cells. Thus, the myocardium may share the central nervous system's sensitivity to T4. (10)

T3 and T4 are "sensed" by the hypothalamus and pituitary and negatively affect secretion of TRH and TSH respectively. Thus, the feedback loop of the hypothalamic-pituitary-thyroid axis is completed.(11)

Thyroid Hormone Function:

The purpose of thyroid hormone is to regulate gene transcription. Upon entering a target cell, T3 binds the thyroid hormone receptor (THR), a member of the steroid hormone superfamily. Bound THR, in turn, forms an association with another protein, the retinoic x receptor (RXR). This heterodimer is then capable of binding to sequences of DNA that are located upstream of the regulated gene. The binding site of the THR-RXR complex is called the thyroid response element, or TRE. The TRE is typically a short sequence of DNA, approximately 10 bases in length. Once bound to the TRE, T3-THR stimulates unfolding of the chromatin structure and transcription of the target gene. In the absence of ligand, the THR can bind to the TRE and suppress transcription. (12)



Which genes are regulated by T3? This is tissue-specific. Each organ system utilizes T3-THR binding to the TRE to mediate transcription of a variety of genes. These gene products serve a number of functions from structural functions to being regulatory proteins themselves.(13) The diverse functions of the genes regulated and the tissue-specific nature of T3 genomic effects explain why individuals with thyroid dysfunction have so many and diverse physical complaints. Virtually every organ system in the body is affected in some manner by abnormal levels of thyroid hormone.

Thyroid Hormone and Cardiac Myocytes:

Like other tissues, the heart utilizes thyroid hormone for regulation of a number of genes: (12)

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)	

Klein and Danzi, Circulation 2007; 116: 1725-1735

Cardiac muscle is dependent on the cycling of cytoplasmic calcium for muscle contraction and relaxation. Calcium is stored in the sarcoplasmic reticulum (SR) and released into the cytosol upon membrane depolarization. This rise in calcium allows the actin and myosin filaments to associate, facilitating muscle contraction during systole. In contrast, myocellular relaxation (diastole) requires sequestration of the cytosolic calcium into the SR. This flux of calcium relies on an ATP-dependent calcium ion channel encoded by the SERCa2 gene and its inhibitor, phospholamban. Thyroid hormone regulates both genes. T3 markedly enhances SERCa2 gene transcription, yet negatively regulates phospholamban. (6, 14, 15) Alteration of expression of these genes inhibits the normal reuptake of intracellular myocardial calcium in the hypothyroid state leading to impairment of diastolic function.

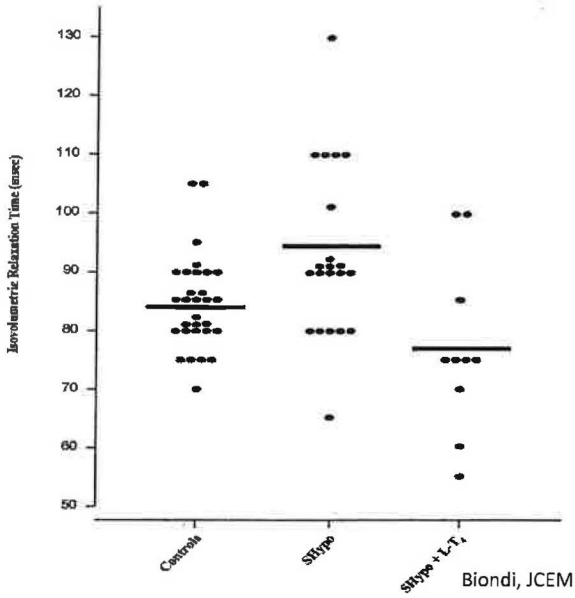
Evidence for alterations in calcium efflux from the SR during systole also exists. The ryanodine channel present on the SR membrane allows for release of calcium during systole. This channel is upregulated in the presence of thyroid hormone. (6) Arai and colleagues demonstrated increased expression of ryanodine channels in the rabbit heart when given supraphysiologic doses of levothyroxine that was reversed by propylthiouracil (PTU). (16) Additionally, The Na/K ATPase on the sarcolemma influences intracellular calcium. The expression of the alpha-1, alpha-2 and beta-subunits are positively regulated by thyroid hormone and may contribute to the alterations of calcium handling in the setting of thyroid dysfunction. (6)

As is clinically apparent in hyperthyroid individuals, thyroid hormone is a positive chronotrope. Although there is evidence that thyroid hormone positively regulates voltage-gated ion channels (12), it has been proposed that the heart rate effects of T3 are too rapid to be mediated by gene expression. (17) It thus appears there are both genomic and non-genomic effects of thyroid hormone on heart rate though the precise mechanism(s) is unclear. Despite mimicking the hyperadrenergic state, there is no evidence to suggest the heart is more or less sensitive to adrenergic stimuli in the setting of thyroid dysfunction.(12)

Hemodynamic Effects of Thyroid Dysfunction:

Hypothyroidism has a variety of hemodynamic effects. As a consequence of thyroid hormone deficiency, alterations of cardiac and peripheral vascular function can occur. Patients with overt hypothyroidism may have significantly impaired systolic and diastolic cardiac function, increased systemic vascular resistance (SVR) and reduced cardiac output. Initially, the increase in SVR outweighs the reduction in cardiac output, hence hypertension is common. However, in advanced hypothyroidism, cardiac output deteriorates due to a combination of reduced contractility and impaired diastolic relaxation. If not corrected, a decompensated state of severe thyroid hormone deficiency characterized by cardiovascular collapse and death may occur. (18)

In subclinical hypothyroidism, much milder but similar hemodynamic effects have been observed. (19) Biondi et al utilized echocardiography to evaluate cardiac function in 26 individuals with SH (24 were women, mean age 36). Compared to controls, measurements of diastolic function, E/A ratio and isovolumetric relaxation time, showed significant impairment. These differences were no longer seen after 6 months of levothyroxine therapy. Other groups have found similar results. (20-24) Faber et al evaluated 16 women with SH (mean TSH 17.1 mIU/L, mean age 60) and measured baseline cardiac output by way of impedance cardiography. (25) SVR was calculated after measurement of mean arterial pressure. All participants were treated with levothyroxine to normalize TSH and hemodynamic parameters were re-measured. Treatment with levothyroxine was associated with a significant reduction in supine mean arterial pressure and SVR. Additionally, a 13% increase in upright cardiac output was observed.



Biondi, JCEM 1999

TABLE 1. HEMODYNAMIC PARAMETERS IN SUBCLINICAL HYPOTHYROIDISM (n = 16), MEAN ± SD

	Supine		*Upright*	
	Before LT_4	*During LT_4*	*Before LT_4*	*During LT_4*
MAP (mm Hg)	101 ± 15.2	94.5 ± 14.5[a]	100 ± 15.5	98.2 ± 14
SV/PP (mL/mm Hg)	1.58 ± 0.78	1.73 ± 0.65	1.32 ± 0.62	1.40 ± 0.58
CO (L/min)	5.93 ± 1.46	6.69 ± 2.04 (p = 0.10)	5.03 ± 1.24	5.74 ± 1.35[b]
CI (L/min/m^2)	3.43 ± 0.77	3.83 ± 1.16 (p = 0.10)	2.88 ± 0.76	3.08 ± 0.97[b]
SVR (dyn * s * cm^{-5})	1465 ± 580	1272 ± 597[b]	1852 ± 779	1474 ± 524[b]

[a]$p < 0.01$, [b]$p < 0.05$, as compared to before LT_4 substitution.
MAP, mean arterial pressure; SV/PP, stroke volume/pulse pressure; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance; LT_4, levothyroxine; SD, standard deviation.

Faber et al Thyroid 2002; 12(4)

The increase in vascular resistance seen in thyroid deficiency has multiple potential mechanisms. First, there is decreased tissue thermogenicity as a result of reduced cellular metabolism. Second, T3 appears to have a direct effect on vascular smooth muscle (26) and indirectly via increased activity of nitric oxide synthase. (10) Thus, the vasculature may have a reduced quantity of nitric oxide and impaired vascular smooth muscle relaxation in the setting of low T3 levels leading to aortic stiffness. (27)

The association of hypothyroidism with hypertension has been noted for many years. Thompson et al first reported this association in 1931. (28) The increase in SVR and impaired

diastolic myocardial relaxation have been implicated in the 30% incidence of diastolic hypertension in persons with OH. (12) It remains unclear whether there is an increased prevalence of hypertension in the setting of SH as there have been conflicting reports. (29-32) These studies have differed in gender and ethnic cohorts studied. Furthermore, well-designed, randomized controlled trials of thyroid hormone replacement with blood pressure as an endpoint have not been done.

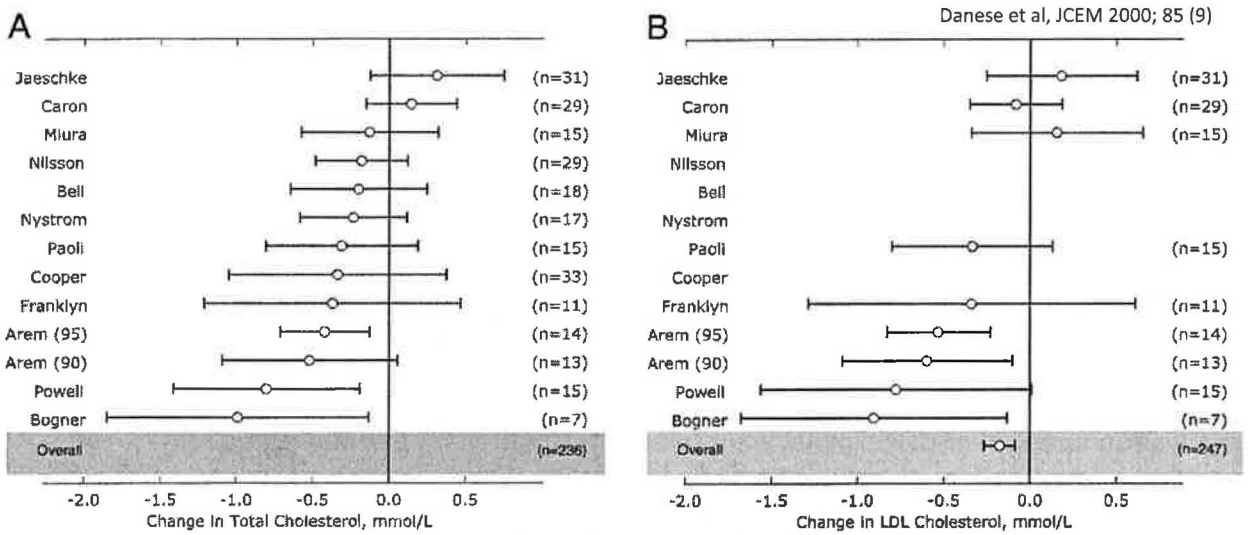
Subclinical Hypothyroidism as a Cardiac Risk Factor (CRF):

In the 1930s, a link between thyroid hormone and serum cholesterol levels was identified. K.B. Turner and colleagues at Columbia University carried out a series of investigations culminating in the observation that serum cholesterol levels increased nearly 20% in thyroidectomized rabbits. (33)

Thyroid hormone plays an active role in lipid physiology. There are several mechanisms by which T3 affects circulating lipid levels. First, thyroid hormone is a regulator of HMG Co-a reductase, the rate-limiting step in cholesterol biosynthesis. (34) Second, a TRE is known to be located in the promoter region of the sterol-regulatory element binding protein 2 (SREBP2) gene. (35) SREBP2, in turn, regulates expression of the LDL receptor. (36) Third, T3 has also been shown to regulate lipoprotein lipase and hepatic lipase, responsible for the hydrolysis of triglycerides. (6, 36, 37) Fourth, thyroid hormone positively influences the activity of cholesteryl-ester transfer protein (CETP) (38) which is responsible for the flux of cholesterol from HDL to VLDL and triglycerides in the opposite direction.

Overt hypothyroidism is a well-known cause of hyperlipidemia. Lipid panels in these individuals typically have elevated total, low-density lipoprotein (LDL) cholesterol and triglyceride levels. (39) This is due to accumulation of LDL, intermediate-density lipoprotein (IDL) and very-low density lipoproteins (VLDL). (40) Although the hepatic biosynthesis of cholesterol is reduced in the hypothyroid state, the reduction in LDL clearance due to lower expression of the LDL receptor predominates.(34) Thyroid hormone replacement in overt hypothyroidism has shown significant reduction in serum cholesterol. (41) Evaluation for thyroid dysfunction has been advocated by the National Cholesterol Education Program (NCEP) report for the evaluation of hyperlipidemia in adults. (42)

Studies evaluating subclinical hypothyroidism as a cause for hyperlipidemia have been conflicting. (3, 43, 44) The Colorado Heart Study demonstrated that total cholesterol levels increased linearly with TSH even within normal TSH ranges. (3) A study from the NHANES III database, however, showed no effect of SH on serum cholesterol, LDL or HDL once data was adjusted for potential confounders. (44) Thus, it is not surprising that the use of levothyroxine



in SCH individuals has also demonstrated conflicting results. Danese et al conducted a metaanalysis that included 13 studies addressing the effect of levothyroxine therapy on serum lipids in SH. Overall, a 7.9 mg/dL decrease in total (95% CI -3.3 to -13) and a 10 mg/dL decrease in LDL cholesterol levels (95% CI -4.0 to -16) was reported. (45)

It has been argued, however, that the Danese study was plagued by small studies, heterogeneous groups and poor data quality. (46) A recent Cochrane analysis reviewed six studies and found no significant effect of thyroid hormone replacement on LDL cholesterol in subclinical hypothyroidism. (46) It was noted however that comparisons were hampered by the large variance in baseline LDL values in the studies included.

It should be stated that cigarette smoking, in concert with SH, may have a synergistically deleterious effect on serum lipid profiles. Muller et al reported that of 84 women with SH in their cohort, the women who smoked had significantly higher TSH values than non-smokers. Similarly, the women who smoked had higher total and LDL cholesterol levels (16% and 25% respectively). (47) No significant difference in lipid levels were seen between smokers and nonsmokers in the euthyroid control group suggesting that smoking had the effect of augmenting the abnormal lipid parameters of thyroid dysfunction.

Endothelial function may also be abnormal in the setting of thyroid dysfunction. Nitric oxide (NO) is a potent vasodilator produced in the endothelium via nitric oxide synthase. Animal data suggests that both production and sensitivity to NO are impaired in hyothyroidism. (48) In humans, forearm strain-gauge plethysmography measures NO-dependent vasodilation and is used as a marker of endothelial function. (49) Studies utilizing this technique have demonstrated impairment of vasodilatory responses in SH individuals. (49-51) In these studies, treatment with levothyroxine reversed these changes. As endothelial dysfunction has been associated with the development of atherosclerosis and marker of increased risk of cardiovascular events (49), this may be another link between mild thyroid failure and IHD.

Carotid intima-medial thickness (CIMT) has been utilized as a surrogate marker for atherosclerosis in clinical research. (52) Investigations into the association of CIMT and thyroid dysfunction have included overtly hypothyroid individuals (53) and SH (54). Baseline CIMT measurements in overtly hypothyroid individuals are higher than euthyroid controls with subclinically hypothyroid individuals demonstrating intermediate values. (54) In one study, after treatment with levothyroxine for 18 months, CIMT was significantly reduced compared to baseline. Statistically, this effect was dependent on reduction of LDL cholesterol values but not the extent of reduction of TSH. Thus, the benefit of CIMT reduction in SH appeared to be chiefly a result of improved lipid parameters. It should be noted that in this study, the mean age was 36 and 86% of participants were female, a traditionally low-risk group for atherosclerotic disease. Whether a more substantial effect would be observed in higher-risk individuals has not been explored.

Lastly, subclinical hypothyroidism has been linked to other potential markers of increased cardiovascular risk such as hyperhomocysteinemia (55), elevated C-reactive protein (56, 57). Whether or not treatment of SH impacts these markers substantially, and by these mechanisms, impacts the incidence of CV disease remains unknown.

Association of SH and ischemic heart disease (IHD):

Studies evaluating a potential link between SH and IHD have been conflicting. (58, 59) Hak utilized the Rotterdam database to assess the prevalence of aortic atherosclerosis and myocardial infarction (MI) in women with subclinical hypothyroidism. Compared with euthyroid individuals, SH women had an OR of 1.7 (95% CI 1.1 to 2.6) and 3.1 (95% CI 1.5 to 6.3) for atherosclerosis and MI respectively. (59) This study was limited by the cross-sectional design and follow-up data that was of relatively short interval (4 years). Razvi and colleagues in Gateshead, UK reported on this association based on the Whickham Survey, a large, cross-sectional population-based cohort followed for 20 years. 2376 individuals with TSH values between 6-15 mIU/L and normal serum T4 levels were analyzed. An adjusted HR of 1.76 (95% CI 1.15 to 2.71) was noted for IHD. IHD-related death was also greater in the SH group [HR 1.79 (95% CI 1.02 to 3.56)]. (60)

As many trials were small or limited to certain demographics, Rodondi and colleagues published a meta-analysis of 11 studies including 3450 individuals with SH. (61) The focus of the analysis was SH as a risk for IHD event, IHD-related and all-cause mortality. The risk of IHD events and IHD-related death increased with increasing TSH and was significantly elevated in individuals with TSH values > 10 mIU/L. This association remained significant after adjustment for age, gender, ethnicity and traditional cardiac risk factors.

TSH (mIU/L)	Coronary Events		Coronary Mortality		All-cause Mortality	
	n	OR	n	OR	n	OR
4.5-6.9	264/1344	1.01 (0.86-1.18)	132/2363	1.06 (0.88-1.28)	640/2431	1.07 (0.96-1.20)
7.0-9.9	96/441	1.22 (0.99-1.49)	50/652	1.53* (1.13-2.07)	170/672	1.11 (0.92-1.33)
10-19.9	70/235	1.86* (1.22-2.82)	28/333	1.54* (1.07-2.23)	105/347	1.24 (0.82-1.87)
P for trend		0.002*		0.005*		0.29

Adapted from Rodondi et al 2010 JAMA

In contrast, the Leiden 85-plus study, following 599 individuals born in 1912-1914 did not find an association between elevated TSH and CV-related mortality. In fact, a higher TSH was associated with a significantly longer lifespan [adjusted HR 0.77 (95% CI 0.63 to 0.94)]. (62) Although this represents an extremely elderly group, the implication is that at some age, the age-related rise in TSH values may cease to be detrimental and become beneficial. It has been proposed that such a "switch" could be related to decreased metabolic demands, or that more traditional cardiac risk factors may mask the effect of SH on IHD. (62, 63)

Impact of Thyroid Hormone Replacement on Incidence of IHD:

To date, there are no randomized, prospective clinical trials assessing the impact of thyroid hormone replacement on cardiac outcomes in SH. Recently, a longitudinal evaluating levothyroxine therapy for subclinical hypothyroidism has been published from the United Kingdom General Practitioner Research Database (GPRD). (64) This database contains information regarding approximately 16% of the UK population. The primary outcome was a composite of fatal and nonfatal CV events. Participants were divided into a younger group aged 40-70 (n=3093) and those older than 70 years (n=1642) by study design. During the 7.6 year follow-up period, approximately half of persons in each group had been started on LT4.

After adjustment of age, gender, traditional cardiac risk factors and levothyroxine use as a time-dependent covariant, the HR for the primary endpoint among levothyroxine-treated individuals

was 0.61 (95% CI 0.39 to 0.95) for the younger group and 0.99 (95% CI 0.59 to 1.33) in the older group.

Table 4. Fatal and Nonfatal Ischemic Heart Disease Events by Age Deciles in Levothyroxine Sodium–Treated and Untreated Individuals With Subclinical Hypothyroidism

	Patients, No. (%)		Events, No. (%)		
Age Group, y	Treated	Untreated	Treated	Untreated	HR* (95% CI)
40-50	433	384	8 (1.8)	9 (2.3)	0.86 (0.09-18.92)
51-60	642	576	24 (3.7)	29 (5.0)	0.43 (0.16-1.15)
61-70	560	498	22 (3.9)	43 (8.6)	0.41 (0.17-0.97)
71-80	504	454	48 (9.5)	29 (6.4)	1.06 (0.62-1.70)
81-90	268	296	35 (13.1)	28 (9.5)	1.36 (0.57-3.20)
91-107	51	66	4 (7.8)	5 (7.6)	1.67 (0.09-31.4)

Similarly, all-cause mortality was lower among levothyroxine-treated cohort in the younger group, whereas the treated, older participants did not derive a mortality benefit. (64)

Impact on Symptoms of Hypothyroidism:

The symptoms of subclinical hypothyroidism are not specific to thyroid dysfunction and are often more subtle than in overtly hypothyroid individuals. The Colorado Heart Study noted a prevalence of hypothyroid symptoms in SH that was intermediate between euthyroid and overtly hypothyroid states. (3) A recent meta-analysis of levothyroxine therapy in SH failed to show a benefit in regards to mood, symptoms or health-related quality of life measures. Indeed, in individuals older than 70 years of age, SH was associated with increased walking speed and overall physical function. (27, 65)

Words from the Societies:

In 2002, the Endocrine Society, the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) created a consensus panel to review the available data on SH. The result of their findings was published in JAMA in 2004. (4) At that time the committee concluded that SH could only be credibly linked to two outcomes: as a predictor of developing overt hypothyroidism, and as a contributor to elevated total and LDL cholesterol in persons with a TSH level of > 10 mIU/L. Thus, it was recommended to treat individuals with TSH > 10 mIU/L with levothyroxine. This report recommended against routine treatment of individuals with TSH levels between 4 and 10 mIU/L.

At this point, an interesting event occurred. Several leading members of the three societies that commissioned the committee disagreed with its recommendations. Hence in 2005, a position statement of the Endocrine Society, AACE and ATA was published. (5) In this report, the authors concluded that most patients with TSH levels between 4 and 10 mIU/L should be considered for treatment and agreed that it would be reasonable to treat all persons with TSH values > 10 mIU/L.

The conflicting statements issued above are not a result of differences in quality or quantity of data reviewed but more of a difference in philosophy. The 2004 committee chaired by Dr. Surks held the belief that treatment should not be administered to individuals with subclinical hypothyroidism (with TSH in range of 4-10 mIU/L) based on the absence of a proven benefit. (4) In contrast, Dr. Gharib, the lead author in the position statement published in 2005 noted that "lack of definitive evidence for a benefit does not equate to evidence for lack of benefit."(5)

Conclusions:

Hypothyroidism is a continuum extending from mild, asymptomatic disease to severe and life-threatening. Subclinical hypothyroidism is a situation in which the TSH value is elevated above normal, but the free thyroxine level is normal. Often patients have minimal or no symptoms. SH has previously been viewed as a biochemical scenario in which the TSH elevation compensates for the thyroid insufficiency. However, our knowledge of the effects of subclinical hypothyroidism on the heart suggest that this compensation is not complete. Thus, subclinical hypothyroidism should be viewed as mild thyroid failure, not merely a laboratory phenomenon.

Subclinical hypothyroidism is associated with diastolic and endothelial dysfunction, and thyroid hormone replacement reverses these changes. Though hypertension and hyperlipidemia may result from SH, studies evaluating the impact of levothyroxine on these parameters in mild SH have been conflicting. It remains unknown whether thyroid hormone replacement will ultimately have a beneficial impact on cardiovascular outcomes in individuals with SH, though a recent large population study showed a significant reduction in both fatal and nonfatal ischemic events with treatment.

Conflicting recommendations from the specialty groups underscore the controversy of managing patients with mild SH (i.e. TSH 4-10). For now, therapy in this group must remain individualized. The clinician should consider the presence of other cardiac risk factors, age and patient preference when making a decision on treatment. Fortunately, the risk of therapy and individual costs associated with levothyroxine therapy are relatively small though a large-scale cost-benefit analysis has not been done. It is reasonable to suggest treatment in persons with cardiovascular risk factors, or who have symptoms of hypothyroidism and are younger than 70 years. Based on the UK-GPRD study, therapy should probably not be advised in persons over 70 unless the TSH is above 10 mIU/L. Prospective studies evaluating the benefit of levothyroxine in subclinical hypothyroidism is needed.

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