# Hypothyroidism – What You Need To Know

**Number of Contact Hours – 2**

**Audience RN**

**Pharmacology Hr : 0**

**CERP : A**

**Goals and Objectives**

Goals

The goal of this article is to review the effects of hypothyroidism and various treatment strategies

Objectives

Discuss the cardiometabolic changes associated with hypothyroidism

Describe the association between hypothyroidism and heart failure

Identify two types of congenital hypothyroidism

Discuss how hypothyroidism affects the heart

Describe the effect of hypothyroid treatment on heart

**Introduction**

Hypothyroidism affects between 4% and 10% of the population, and the prevalence of subclinical hypothyroidism is reported to be as high as 10% in various studies. Hypothyroidism is diagnosed when low levels of the thyroid hormones result in elevated levels of thyroid-stimulating hormone (TSH), whereas subclinical hypothyroidism is diagnosed when TSH levels are elevated above the upper limit of the assay reference range with normal thyroid hormone levels. Thyroid hormones play an important role in the normal function of heart and vascular physiology, and hypothyroidism produces profound cardiovascular effects. Of recent clinical interest is the effect of subclinical hypothyroidism on cardiovascular disease and whether or not it should be treated. [1, Rank 4]

**Cardiometabolic Changes in Hypothyroidism**

Thyroid hormones have a variety of effects on the cardiovascular system that can greatly impact cardiac function. Hypothyroidism is associated with decreased cardiac output due to impaired relaxation of vascular smooth muscle and decreased availability of endothelial nitric oxide. This produces a cascade effect of increased arterial stiffness that leads to increased systemic vascular resistance. On a molecular level, these alterations result from reduced expression of sarcoplasmic reticulum $Ca^{2+}$-ATPase and increased expression of phospholamban, which inhibits ATPase. Thyroid hormones also impact the renin-angiotensin-aldosterone system. Renin substrates are synthesized in the liver under the stimulus of T3. Thus, in a hypothyroid state, diastolic blood pressure increases, pulse pressure narrows, and renin levels decrease. This results in diastolic hypertension that is often sodium sensitive. Erythropoietin secretion is increased by T3, which can explain the normochromic, normocytic anemia often found in hypothyroidism. Thyroid hormones also regulate pacemaker-related genes through transcription as well as the beta-adrenergic system in cardiomyocytes. As a result of these mechanisms, heart rate increases in the presence of thyroid hormones and decreases in hypothyroidism. Varied alterations in lipid parameters are noted in both overt and subclinical hypothyroidism, including elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B. A hypothyroid state results in decreased expression of hepatic LDL receptors and reduced activity of cholesterol-α-monooxygenase, which breaks down cholesterol, resulting in decreased LDL clearance. Also noted are elevations in both C-reactive protein and homocysteine. Thyroid hormones affect endothelial functions mediated by thyroid hormone receptor (THR)-$\alpha_1$ and THR-β. Activation of THR-$\alpha_1$ increases coronary blood flow, decreases coronary resistance in mouse models, and increases production of nitric oxide in endothelial and vascular smooth muscle cells. Thyroid hormone activation of THR-β induces angiogenesis by initiating the mitogen-activated protein kinase pathway. Severe hypothyroidism can also cause pericardial effusion. Though the mechanism is unclear, increased capillary permeability and reduced lymphatic drainage from the pericardial space have been suggested. Hypothyroidism can also be associated with a decrease in insulin sensitivity due to downregulation of glucose transporters and direct effects on insulin secretion and clearance.

**Heart Failure and Hypothyroidism**

Hypothyroidism can affect cardiac contractility, which is often diastolic in nature, and impair cardiac muscle relaxation. Associated diastolic hypertension and sometimes-coexistent coronary artery disease further affect myocardial diastolic function. Cardiac echocardiography has demonstrated impaired relaxation in patients with overt and subclinical hypothyroidism. In addition, early impaired relaxation has been demonstrated by prolongation of the isovolumetric relaxation time and reduction in the E/A ratio in subclinical hypothyroidism. The E/A ratio is a ratio of early to late ventricular filling velocities, and a reduced E/A ratio signifies diastolic dysfunction from impaired relaxation. Consequently, it results in a state of low cardiac output with decreased heart rate and

stroke volume. It is well known that protein-rich pericardial and/or pleural effusion often occurs in hypothyroidism as a result of increased vascular permeability. In advanced heart failure and shortly after myocardial infarction, the conversion of T4 to T3 decreases. Since T3 is the main regulator of gene expression in myocardial muscle, this decrease has been thought to affect myocardial contractility and remodeling. Low free T3 levels also have been associated with increased mortality in patients with heart disease.

It is well known that hyperthyroidism is associated with atrial fibrillation (AF). Similarly, hypothyroidism is associated with increased cardiovascular risk factors as well as subclinical and diagnosed cardiovascular disease, both of which are thought to predispose one to AF. However, the relationship between hypothyroidism and AF was evaluated in the Framingham Heart Study and was not found to be statistically significant. The QT interval is often prolonged in hypothyroidism due to prolonged ventricular action potential. This is indicative of increased ventricular irritability and in turn can lead to acquired Torsades de pointes. Varying degrees of atrioventricular block and low QRS complexes are also seen in patients with hypothyroidism. Generally, the incidence of ventricular fibrillation is decreased in hypothyroidism, and depression of thyroid hormone levels appears to be beneficial in patients with angina and acute myocardial infarction. Bradycardia can be beneficial as it raises the arrhythmogenic threshold, especially in patients with underlying cardiovascular disease. In summary, unlike hyperthyroidism, hypothyroidism is linked with a decreased probability of cardiac arrhythmias.

Amiodarone is an iodine-rich benzofuranic compound that is used to manage cardiac arrhythmias. It contains about 37% iodine by weight, and a 200-mg dose exposes the patient to about 300 times the recommended daily allowance. Due to its lipophilic nature, it concentrates in several tissues and organs, including the thyroid gland. Its active dealkylated metabolite, desethylamiodarone, tends to have a half-life of about 57 days, thus effects can be long-lasting even after discontinuation. Amiodarone-induced thyroid dysfunction could be secondary to iodine load or intrinsic effects of amiodarone itself. The iodine load from amiodarone can result in amiodarone-induced hypothyroidism (AIH) by inhibiting the oxidation of iodine, known as the Wolff-Chaikoff effect. This is particularly the case in patients with underlying or preexisting thyroid disease such as goiter or autoimmune thyroid disease.

Amiodarone by itself can also affect deiodinase activity. In vivo, it inhibits deiodinase-1 activity and pituitary deiodinase-2 activity, resulting in high T4, high reverse T3, and low T3. This may spur an initial increase in TSH that often returns to baseline in 2 to 3 months. With long-term treatment, TSH usually normalizes with total and free T4 and reverse T3 levels that remain slightly elevated. Early AIH may be present in 10% to 20% of patients treated with amiodarone, whereas the incidence with long-term treatment is often lower, from 5% to 10%. AIH is noted to be more frequent in iodine-sufficient areas of the world, and the presence of thyroid autoantibodies is associated with an increased likelihood of developing

AIH. There is also an understanding that amiodarone may hasten the pathogenesis of Hashimoto thyroiditis. Since AIH manifests as primary hypothyroidism, diagnosis is similar to primary hypothyroidism, as is treatment with levothyroxine replacement. [3, Rank 3]

**Hypothyroidism and the Heart**

Subclinical hypothyroidism is biochemically defined as a TSH level above the upper limit of the reference range with normal thyroid hormone levels. Severity of subclinical hypothyroidism is further defined based on the elevation in TSH levels, where mildly increased serum TSH levels range from 4 mIU/L to 10 mIU/L, and anything above 10 mIU/L indicates severely increased TSH levels. The reported prevalence of subclinical hypothyroidism depends on several factors, such as iodine supplementation, age, and race. In the United States, the prevalence of subclinical hypothyroidism is reported as 4.3% in the NHANES III study and as high as 9.5% in the Colorado study. The annual risk of progression to overt hypothyroidism is reported at 1% to 5%, depending on TSH levels and thyroid antibody status. Up to 60% of patients with subclinical hypothyroidism can return to euthyroidism over 5 years, again based on TSH levels and antibody status. As described earlier, cardiovascular changes of arterial compliance, diastolic blood pressure, endothelial dysfunction, and hyperlipidemia that are noted with overt hypothyroidism can also occur in subclinical hypothyroidism.

Researchers have noted a significant association between subclinical hypothyroidism and prevalence of ischemic heart disease in residents after adjusting for age and sex. The association persisted after additional adjustments were made for other factors such as systolic blood pressure, body mass index, total cholesterol, smoking status, erythrocyte sedimentation rate, and diabetes. A Taiwanese study noted an increased risk for all-cause mortality and cardiovascular death in patients with subclinical hypothyroidism. One could argue that radiation exposure may have played a role in the Japanese study. However, reanalysis of the United Kingdom-based Whickham survey noted a significantly higher incidence of ischemic heart disease and related mortality in patients with subclinical hypothyroidism as well. In contrast, the EPIC-Norfolk study did not reveal an increase in coronary heart disease and all-cause mortality across a decade of follow-up. A meta-analysis that included 11 prospective cohorts across five continents noted that subclinical hypothyroidism is associated with an increased risk of coronary heart disease events and mortality with elevated TSH levels, especially in those with values greater than 10 mIU/L. Several of those studies suggested an increased risk of coronary heart disease and cardiovascular mortality and an increased risk of cardiovascular disease in younger individuals with the cut-off age varying from 50 to 70 years.

**Effect of Hypothyroid Treatment on Heart**

Treatment with levothyroxine in those with overt thyroid dysfunction has been shown to improve LDL cholesterol, total cholesterol, triglycerides, hypertension, diastolic dysfunction, heart rate, and heart rate variability in exercise and to delay progression of

atherosclerosis. Patients with cardiomyopathies may demonstrate improved cardiac contractility and stroke volume with levothyroxine treatment. One of the main concerns with starting levothyroxine replacement is the precipitation of myocardial ischemia or arrhythmias, which, although rare, are known to occur. The recommendation for these patients are usually to start with low doses and gradually escalate until euthyroid status is achieved.

In patients with subclinical hypothyroidism, cohort studies have not found significant differences in cholesterol levels or diastolic blood pressures. However, small randomized trials have discovered some beneficial effects of treatment with levothyroxine. In a study of women with subclinical hypothyroidism, 18 months of treatment resulted in normalization of systolic and diastolic blood pressure and of total and LDL cholesterol as well as decreased carotid intima thickness. In another study of patients with subclinical hypothyroidism and coronary artery disease, no significant changes occurred in the group randomized to levothyroxine, but those who received placebo had echocardiographic evidence of progression to myocardial diastolic dysfunction. Although there are no randomized clinical trials evaluating long-term cardiovascular outcomes and mortality in patients treated with levothyroxine, a population-based study of levothyroxine-treated patients demonstrated that those with elevated TSH (defined as greater than 4 mIU/L) had a greater risk for cardiovascular events despite receiving the drug. Analysis from a population-based cohort study revealed that patients with treated hypothyroidism noted no increase in all-cause or cancer mortality but did notice an increase in cardiovascular morbidity in terms of ischemic heart disease and dysrhythmias.

Analysis from the United Kingdom General Practitioner Research Database noted that treatment of subclinical hypothyroidism with levothyroxine was associated with fewer ischemic heart disease events in younger individuals (ages 40–70 years) but not notable in older individuals (> 70 years). Several studies have indicated that levothyroxine treatment in patients with subclinical hypothyroidism has a favorable impact on surrogate markers of vascular disease; however, they do not provide enough confidence that levothyroxine therapy can reverse vascular risk. The 2013 European Thyroid Association guidelines recommend replacement therapy with levothyroxine in patients younger than 65 years of age with serum TSH levels > 10 mIU/L. The guidelines discourage hormone treatment in the oldest patients (> 80–85 years) with TSH values < 10 mIU/L; however, these patients should be carefully monitored. These guidelines further recommend that if treatment of subclinical hypothyroidism is undertaken in patients with cardiac disease and in the elderly, a small dose of levothyroxine (25 or 50 mcg) should be started with gradual titration until a full replacement dose is achieved. [4, Rank 5]

**Hypothyroidism and Primary Open Angle Glaucoma (POAG)**

Glaucoma, which is the major cause of irreversible blindness worldwide, is a complex disorder characterized by progressive optic neuropathy and corresponding visual field

defects. Primary open angle glaucoma (POAG) is the most common form of glaucoma. Nevertheless, the exact mechanism for POAG remains poorly understood, and a great number of patients with POAG have not been diagnosed. Recently, a large number of population-based studies have identified several risk factors associated with POAG, including diabetes, current alcohol consumption, myopia, older age, African ancestry, and a family history of POAG.

Hypothyroidism which affects nearly 10% of the general population and occurs more frequently among those of advanced age is a prevalent endocrine disease characterized by low serum levels of thyroid hormones. Hypothyroidism results in a reduction of cellular metabolism and yields a wide range of overt and subclinical symptoms and signs. It has been hypothesized that the deposition of mucopolysaccharides in the trabecular meshwork in patients with hypothyroidism might result in rising intraocular pressure (IOP). In addition, the treatment of hypothyroidism alone would significantly improve the facility of outflow. Thus, POAG might have a significant association with hypothyroidism. In fact, several epidemiological studies have demonstrated this relationship.

However, there have been contradictory reports in the literature about whether hypothyroidism is independently associated with an increased risk of developing POAG. Subjects with hypothyroidism had a significantly greater risk of developing glaucoma compared with controls. Nevertheless, other studies do not support this effect

Although several risk factors for the development of POAG, such as diabetes, increased age, myopia, and family history of glaucoma have been assessed, this research area remains the subject of ongoing investigation. Early on, in the 1920s, scholars had hypothesized that hypothyroidism was an important risk factor for POAG. They speculated that the low metabolic condition caused by hypothyroidism would lead to decreased enzymatic activity that disadvantageously impacted aqueous humor dynamics. Thus, the belief that a certain relationship between hypothyroidism and POAG might exist has been around for some time.

In order to confirm this potential association, several epidemiological studies have tried but failed to reach a consistent conclusion. Thus, it remains controversial whether or not hypothyroidism increases the risk of POAG. Meta-analysis is a powerful statistical method that allows data on the same topic to be synthesized with greater power to obtain more accurate risk estimations. Meta-analysis was therefore conducted to reach a definite conclusion about the relationship between hypothyroidism and POAG. This study, which was based on 11 previous studies containing a total sample of 381,695 subjects, demonstrated a statistically significant association between hypothyroidism and POAG. Individuals with hypothyroidism were 1.64 times more likely to have POAG than those without hypothyroidism. Subgroup analysis showed that unlike European individuals, North American and Asian individuals had an increased risk of developing POAG. The small sample sizes and resulting insufficient statistical power of the two included studies from Europe might explain this negative association. In addition, it should be noted that in subgroup

analyses of study design, cross-sectional design did not show an association; this might be explained by the significant selection bias the cross-sectional design was subject to. To achieve a reliable and convincing result, a series of analyses were carried out. Sensitivity analyses were conducted, by which the influence of a single study on the pooled effect was examined by removing one study at a time. The results showed that this analysis did not significantly change the global estimation, which supports the reliability of this study. Additionally, publication bias analysis showed a low probability of publication bias in the pooled results, further demonstrating the robustness of the present meta-analysis. [5, Rank 2]

There are some possible mechanisms that could support the notion that hypothyroidism affects susceptibility to and the progression of POAG. One such mechanism is the deposition of mucopolysaccharides and hyaluronic acid in the trabecular meshwork caused by hypothyroidism, which in turn causes an obstruction in outflow that would elevate the IOP. Another potential mechanism might be the increase of outflow resistance in patients with hypothyroidism. Researchers demonstrated this by subconjunctival injection of hyaluronidase in normal and POAG subjects, from which it was determined that outflow resistance was significantly lowered in POAG patients.

This meta-analysis showed that hypothyroidism was observed to significantly increase the risk of POAG, although the substantial heterogeneity between effect size estimates limits the ability to draw firm conclusions. This heterogeneity may reflect different eligibility criteria, study populations, definitions of POAG and hypothyroidism, and/or levels of adjustment for potential confounders. To investigate the sources of heterogeneity, stratified analyses according to study design, geographical area, methods for determining hypothyroidism, publication year, and the number of adjusted variables were performed. However, only slight changes were found, and a high level of heterogeneity remained in most of the subgroups. Then, in the sensitivity procedure, it was found that heterogeneity among the included studies could be attributed to research studies; when these studies were excluded, the remainder showed no evidence of heterogeneity. For one study, several reasons may attribute to the heterogeneity. First, the relative small sample size might be the main source of heterogeneity. In this study, subjects were POAG patients with normal intraocular pressure (IOP) but not IOP ≥ 21 mm H, as other studies reported. Therefore, patient selection might be the second source of heterogeneity. Third, the low incidence of hypothyroidism in all included subjects might be another cause of heterogeneity.

The major strength of this study was that it performed the first meta-analysis to assess the association between hypothyroidism and POAG via an extensive literature search that included as many relevant studies as possible to obtain a more precise conclusion. Another strength of the present study is that the enlarged sample size gave the meta-analysis enhanced statistical power to obtain a more reliable estimation of the association between hypothyroidism and POAG. Lastly, the studies included in this meta-analysis were conducted in different countries, making the results more generalizable.

Several limitations of this study should be acknowledged. First, the diagnosis of hypothyroidism in several of the studies was ascertained based on self-reports, which could cause the misclassification of hypothyroidism patients as non-hypothyroidism subjects. This underestimation might attenuate the true correlation between hypothyroidism and POAG. Second, the sample sizes in some subgroups were too small and had insufficient statistical power to reach a positive association. Third, some of the included studies failed to adjust for common confounding variables known to be risk factors for POAG, which might have affected the pooled results. Fourth, the possibility of publication bias is a major problem in any meta-analysis, because statistically significant results are more likely to be published than those with null results. Nevertheless, we found no evidence of publication bias using Begger's and Egger's tests in this meta-analysis. Finally, significant heterogeneity existed among the studies. Thus, the findings of this meta-analysis should be interpreted with caution.

In conclusion, the findings of this meta-analysis suggest that individuals with hypothyroidism have an increased risk of developing POAG. Given the limitations of this meta-analysis, this conclusion should be interpreted with caution. In the future, both experimental and epidemiological studies are needed to better understand the association between hypothyroidism and POAG. [6, Rank 3]

**Congenital Hypothyroidism**

Primary Congenital Hypothyroidism

Most congenital hypothyroidism is caused by defects in the thyroid gland itself (primary hypothyroidism). Causes of primary congenital hypothyroidism can be broadly classified as failure of the thyroid gland to develop normally (*dysgenesis*) or failure of a structurally normal thyroid gland to produce normal quantities of thyroid hormone (*dyshormonogenesis*). Thyroid dysgenesis—which encompasses the spectrum of thyroid agenesis, hypoplasia, and ectopy—is the most common cause of congenital hypothyroidism, and its incidence (about 1:4000 infants) has not changed significantly over the last several decades. The underlying cause of thyroid dysgenesis, however, remains obscure in the vast majority of cases. Thyroid dysgenesis usually occurs sporadically, with only 2–5% of cases being attributable to identifiable genetic mutations. Nevertheless, the known genetic causes of thyroid dysgenesis provide an important window into basic thyroid ontogeny. The thyroid-stimulating hormone receptor (*TSHR*) and the transcription factors *PAX8*, *NKX2–1*, and *FOXE1* are all expressed in the developing thyroid, and disruption of any of these genes can lead to failure of normal thyroid gland formation. These transcription factors also play important roles in other developing tissues, and mutations in each may be associated with additional syndromic features such as renal abnormalities (*PAX8*), interstitial lung disease and chorea (*NKX2–1*), or cleft palate, bifid epiglottis, choanal atresia, and spiky hair (*FOXE1*)

Several other genes implicated in thyroid dysgenesis offer additional insights into the mechanisms of thyroid development. The transcription factor *NKX2–5* is expressed in the

developing heart and thyroid, and *NKX2–5* mutations are associated with congenital cardiac abnormalities. Deletion of *NKX2–5* in mice causes thyroid agenesis, suggesting that this transcription factor plays an important role in thyroid development, but to what degree this finding extends to humans is not clear. Heterozygous variants in *NKX2–5* are found in some individuals with thyroid dysgenesis; however, the pathogenicity of these variants is unclear since they do not consistently cosegregate with thyroid disease in families and some may not impair protein function in vitro. Therefore, the precise role of *NKX2–5* in thyroid dysgenesis remains to be clarified.

Mutations in *GLIS3* underlie a complex syndrome of congenital hypothyroidism, neonatal diabetes mellitus, and variable other abnormalities including congenital glaucoma, developmental delay, hepatic fibrosis, and polycystic kidneys. *GLIS3* is highly expressed in the thyroid, and congenital hypothyroidism in patients with *GLIS3* mutations may be associated with either thyroid dysgenesis or a eutopic but histologically abnormal thyroid gland. GLIS3 may act as a transcriptional activator or repressor, but its precise role in thyroid development and function remains to be determined. Some patients with *GLIS3* mutations require unusually high doses of levothyroxine to normalize serum thyroid stimulating hormone (TSH) levels, which could imply an additional effect of GLIS3 on central regulation of the hypothalamic-pituitary-thyroid (HPT) axis.

Recently, genetic variants in *CDCA8* (also called *BOREALIN*) were identified in a study of three consanguineous families with thyroid dysgenesis. This gene is expressed in the thyroid and is known to play a key role in the chromosomal passenger complex that stabilizes the mitotic spindle during cell division. Interestingly, however, the *CDCA8* variants detected in these patients do not appear to affect mitosis but rather impair cell migration and adhesion in vitro. Thus, the potential mechanistic role of CDCA8 in thyroid dysgenesis is still unclear, and the range of thyroid phenotypes observed in patients carrying *CDCA8* variants is broad, ranging from thyroid agenesis or ectopy to euthyroid individuals with asymmetric thyroid lobes or thyroid nodules. [7, Rank 4]

While thyroid dysgenesis remains the most common cause of congenital hypothyroidism, the incidence of dyshormonogenesis has been increasing over the last few decades. Whereas dyshormonogenesis accounted for only 15% of congenital hypothyroidism diagnosed in the early days of newborn screening, 30–40% of infants diagnosed by current newborn screening strategies have a eutopic thyroid gland consistent with a form of dyshormonogenesis. While the term *dyshormonogenesis* has classically referred to discrete defects in the cellular machinery of thyroid hormone synthesis leading to (often goitrous) congenital hypothyroidism, increasing recognition of the wide spectrum of severity of such defects makes it reasonable to define dyshormonogenesis as inadequate thyroid hormone production from a eutopic thyroid gland.

Unlike thyroid dysgenesis, in which a monogenic cause is present in only a small minority of patients, dyshormonogenesis is frequently due to a genetic defect in some element of

thyroid hormone synthesis. Known genetic causes of dyshormonogenesis include mutations in thyroglobulin (*TG*), thyroperoxidase (*TPO*), dual oxidase 2 (*DUOX2*) and its accessory protein (*DUOXA2*), the sodium-iodide symporter (*SLC5A5*), pendrin (*SLC26A4*), and iodotyrosine deiodinase (*IYD*). Although dual oxidase 1 (*DUOX1*) is highly homologous to *DUOX2*, isolated defects of *DUOX1* have not been reported to cause congenital hypothyroidism. However, because hypothyroidism due to *DUOX2* mutations tends to be relatively mild, it has been suggested that DUOX1 may partly compensate for DUOX2 deficiency. This hypothesis has been supported by the fact that mice lacking function of both DUOX enzymes have more severe hypothyroidism than those lacking only DUOX2. More recently, the first evidence of a physiologic role for DUOX1 in humans was provided by a report of two siblings with homozygous inactivating mutations in both *DUOX1* and *DUOX2* associated with congenital hypothyroidism more severe than is typically observed in DUOX2 deficiency alone. While further data are needed, it appears that DUOX1 may indeed serve a redundant role in the human thyroid, not being required for thyroid function under normal circumstances but able to partly compensate when DUOX2 function is impaired.

Despite the growing number of genes associated with congenital hypothyroidism, precisely what proportion of congenital hypothyroidism is attributable to known genetic causes and the relative prevalence of mutations in specific genes are not known precisely, and estimates vary among studies. These variations are influenced by several factors including cohort selection that differs in terms of patient ethnicity and the type(s) of congenital hypothyroidism studied, and the sequencing approaches used to detect mutations. With regard to ethnicity, for example, *DUOX2* appears to be the most commonly implicated gene in East Asian populations, with *DUOX2* variants reported in 16–32% of congenital hypothyroidism patients in Korea, Japan, and China. On the other hand, in a cohort of mostly European and Middle Eastern patients, variants in *TG* were much more common (55%) than *DUOX2* variants, which were found in only 18%. However, the latter study was enriched for familial cases of congenital hypothyroidism and is likely to overestimate the prevalence of genetic mutations; therefore, the reported prevalences are likely not generalizable to sporadic cases, which constitute the majority of congenital hypothyroidism seen in clinical practice.

This demographic difference highlights the important influence of cohort selection on the apparent prevalence of genetic mutations in congenital hypothyroidism. Another illustration comes from studies that include patients with congenital hypothyroidism of varying etiologies. For example, one Korean study of 170 infants with congenital hypothyroidism of any etiology found mutations in 31% (most of whom had dyshormonogenesis), while another study from the same country that included only patients with a eutopic thyroid gland identified mutations in 53.5%. Similarly, the prevalence of *DUOX2* variants in Italy has been reported as 15% in unselected patients with congenital hypothyroidism, 23% in those with a eutopic thyroid gland, and to 30–37% in those with a eutopic gland and a

documented partial iodine organification disorder. Thus, more refined cohort selection can significantly increase the observed prevalence of variants in relevant genes and must be considered when interpreting these data.

Finally, as might be expected, recent studies examining larger sets of candidate genes (often using next-generation sequencing techniques) are increasingly identifying potentially causative variants in a higher proportion of patients than older studies that analyzed only one or a few genes. For example, a recent analysis of 11 genes associated with congenital hypothyroidism in 177 Italian patients with congenital hypothyroidism of any cause demonstrated an overall variant prevalence of 58%; the prevalence was even higher (about 75%) in patients with a eutopic thyroid gland. Many patients (23%) harbored variants in more than one gene, similar to other reports. This consistent finding suggests that the apparent lack of heritability of congenital hypothyroidism may be explained by a confluence of rare variants in several genes. On the other hand, while this hypothesis is intriguing, it remains at odds with the observed high rate of discordance for thyroid dysgenesis among monozygotic twins (who share nearly all variants in all genes), which implies that it is unlikely for a significant proportion of congenital hypothyroidism to be explained by germline genetic changes alone. Another limitation of this and similar genetic studies is that the functional significance of many reported variants—particularly novel missense variants—has not been rigorously evaluated; accordingly, a causal role for these variants in congenital hypothyroidism must be imputed cautiously.

Another novel aspect of this study was to analyze variants in genes associated with both thyroid dysgenesis and dyshormonogenesis in all patients, regardless of their thyroid anatomy. Somewhat unexpectedly, variants in genes typically associated with dysgenesis (e.g., *NKX2–1*, *FOXE1*) were found in patients with dyshormonogenesis, and vice versa. This finding highlights the potential overlap in pathogenesis between the classically distinct phenotypes of thyroid dysgenesis and dyshormonogenesis. An example of such cross-over is *JAG1*, which encodes a ligand of the Notch receptor that is critical for normal thyroid gland formation in zebrafish. Recently, anatomic thyroid defects have been found in a series of patients with heterozygous *JAG1* variants, including both patients with classical Alagille syndrome (a multisystem disorder known to be caused by *JAG1* mutations) and patients with congenital hypothyroidism without syndromic features. These variants were confirmed to disrupt JAG1 function in vivo and strongly support a role for JAG1 in thyroid development in humans. Interestingly, however, the etiologies of hypothyroidism in patients with *JAG1* mutations included not only thyroid dysgenesis, as might be expected from the zebrafish model, but also eutopic thyroid glands. Thus, the case of *JAG1* illustrates the complexity of thyroid development and that the genetic abnormalities underlying the phenotypes of thyroid dysgenesis and dyshormonogenesis may overlap to a greater extent than has been previously appreciated. [8, Rank 4]

<u>Central Congenital Hypothyroidism</u>

In contrast to primary disorders of the thyroid gland, central hypothyroidism is caused by dysfunction of hypothalamic or pituitary control of the thyroid axis that leads to inadequate production and/or bioactivity of TSH. Congenital hypothyroidism of central origin is rare: early estimates of its incidence were between 1:29,000 and 1:110,000, although more recent data from the Netherlands suggest that it may occur in as many as 1:16,000 newborns and could represent up to 13% of cases of permanent congenital hypothyroidism. Although this incidence is similar to that of phenylketonuria (1:15,000) - the condition for which newborn screening was originally introduced in the 1960's - central congenital hypothyroidism cannot be detected by the TSH-based screening strategies used by the majority of the newborn screening programs worldwide. Central hypothyroidism may be detected by screening programs that measure T4 concentrations in all infants, along with measurement of TSH either simultaneously or in the subset of infants with low T4. However, this approach may not have optimal sensitivity and may miss some cases of central hypothyroidism.

One argument that has been made against routine screening for central hypothyroidism is that it tends to be milder than primary hypothyroidism and is therefore less critical to identify and treat early. Although developmental delays have been reported in small studies of infants who experienced delayed treatment of central congenital hypothyroidism, there are no data to demonstrate clearly that early treatment improves outcomes in infants with this condition. However, indirect evidence may be derived from studies of primary congenital hypothyroidism, in which the initial serum concentration of total or free thyroxine (FT4) is one of the most important and consistent predictors of neurodevelopmental outcome. In light of this, the premise that central congenital hypothyroidism poses less developmental risk has been challenged by a recent study from the Netherlands demonstrating that 55% of newborns with central hypothyroidism detected on newborn screening had FT4 concentrations sufficiently low (< 10 pmol/L) to warrant treatment according to current consensus guidelines. While few of these patients had the severely low FT4 levels often seen in primary congenital hypothyroidism, their FT4 levels were reduced to a range (5–10 pmol/L) that has been associated with modest deficits at age 10 years. Thus, it appears that a substantial proportion of infants with central congenital hypothyroidism may be at some developmental risk if undetected and untreated, although the precise extent of this risk remains to be determined. [9, Rank 3]

In addition, 75% of infants with central congenital hypothyroidism have additional, potentially life-threatening pituitary hormone deficiencies such as adrenal insufficiency and growth hormone deficiency, and detection of these comorbidities represents another argument in favor of screening for central hypothyroidism. Moreover, some have suggested that a carefully designed T4-based screening strategy able to detect these infants may actually be more cost effective than TSH-based screening. In summary, while arguments can be made for routine newborn screening for central hypothyroidism, more compelling

evidence is needed to support the need for and feasibility of widespread implementation of such strategies.

Despite its rarity, central congenital hypothyroidism provides an important window into the ontology and physiology of the HPT axis. Normally, thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates thyrotropes in the anterior pituitary to secrete TSH. Congenital defects in this system result from abnormal development of the hypothalamus or pituitary or from genetic alterations that impair the function of TRH or TSH. Developmental or structural anomalies often have broad effects on the hypothalamus and/or pituitary that lead to deficits in multiple pituitary hormones. While some of these cases have no identifiable genetic basis, others can be attributed to mutations in one of several genes critical for the normal early development of these structures, including *HESX1*, *LHX3*, *LHX4*, *SOX3*, and *OTX2*. These transcription factors have broad effects on fetal development and each is associated with particular syndromic features in addition to combined pituitary hormone deficiency. In contrast, the transcription factors *PROP1* and *POU1F1* are expressed later in anterior pituitary differentiation and their disruption results in combined pituitary hormone deficiency without other syndromic features.

While central developmental abnormalities often affect multiple pituitary hormones, specific defects in TRH or TSH signaling lead to isolated central congenital hypothyroidism. Until recently the only known genetic causes of this condition were very rare mutations in the TRH receptor (*TRHR*) or the TSH β-subunit (*TSHB*). However, in 2012 a study of 11 families with central congenital hypothyroidism identified a novel X-linked cause of central hypothyroidism, *IGSF1*. Numerous cases of IGSF1 deficiency have since been described, making it the most common identifiable genetic cause of isolated central congenital hypothyroidism.

In addition to central hypothyroidism, males carrying an inactivating mutation of *IGSF1* manifest a clinical syndrome that includes macro-orchidism (88% of patients) and variable hypoprolactinemia (60% of patients). Testicular enlargement can begin before the onset of puberty and has been observed as early as 3 years of age, and affected adults may have testicular volumes up to 45–50 mL. While the normal pubertal increase in testicular size is accelerated in affected individuals, the pubertal rise in testosterone levels appears to be delayed, and plasma testosterone levels remain in the low-normal range in adults. A few children also appear to have transient growth hormone deficiency that resolves by adulthood. Importantly, although the IGSF1 deficiency syndrome is X-linked, 18% of female mutation carriers have central hypothyroidism, about 20% have biochemical prolactin deficiency (although lactation is apparently normal), and up to one-third have late menarche.

At the time of its discovery *IGSF1* was known to encode a plasma membrane glycoprotein expressed in anterior pituitary thyrotropes, but its function was unknown. Recently, two

studies have begun to elucidate the role of *IGSF1* in the HPT axis and a potential mechanism by which it may cause central hypothyroidism. Both humans and mice deficient in IGSF1 show impaired secretion of TSH in response to exogenous TRH administration, implying a functional defect in TRH signaling. Further studies indicate that IGSF1 directly stimulates TRHR activity in cell culture, while Igsf1-deficient mice have reduced pituitary TRHR expression and increased hypothalamic TRH expression. Thus, both in vitro and in vivo evidence suggest that IGSF1 deficiency may cause central hypothyroidism by impairing expression and downstream signaling of the TRH receptor in pituitary thyrotropes. One mechanism by which IGSF1 may promote TRHR signaling is by blocking the inhibitory effect of TGFβ on TRHR expression. Absence of IGSF1 may permit excessive TGFβ-mediated suppression of TRHR that leads to central hypothyroidism. Interestingly, IGSF1 appears to have the opposite effect in pituitary gonadotropes of decreasing FSH β-subunit (*FSHB*) expression. Loss of this inhibition and consequent oversecretion of FSH might explain the macro-orchidism observed in males with IGSF1 deficiency. IGSF1 is also expressed in the Leydig cells and germ cells of the testis, where its role remains uncertain. While more research is needed to understand the mechanisms of IGSF1 action, its discovery has opened the door to the study of novel biology in both the thyroid and gonadal axes.

Recently, mutations in *TBL1X* have been found in several families with X-linked central hypothyroidism. This gene is expressed in the human pituitary and the paraventricular nucleus of the hypothalamus (where TRH-secreting neurons are located), and it encodes a protein that is part of the NCoR-SMRT corepressor complex, a key regulator of thyroid hormone-dependent gene expression. A pathogenic role for TBL1X defects is supported by a mouse model in which impaired NCoR function causes central hypothyroidism, and further investigation of the potential role of *TBL1X* in central hypothyroidism is now needed. [10, Rank 4]

<u>Mild Congenital Hypothyroidism</u>

As previously noted, most newborn screening programs around the world use TSH-based strategies that effectively detect the vast majority of congenital hypothyroidism. Over the past 30 years, many programs have lowered their screening TSH cut-offs from 20 - 50 mIU/L to 6–15 mIU/L. These changes have resulted in the diagnosis of many more patients with mild congenital hypothyroidism, most of whom have a eutopic thyroid gland. However, in contrast to the known neurodevelopmental risks of severe congenital hypothyroidism and the obvious benefits conferred by its timely and adequate treatment, much less is known about the risks posed by the milder forms of congenital hypothyroidism that are increasingly being diagnosed. This uncertainty is reflected in current consensus guidelines, which find insufficient evidence to recommend for or against the treatment of infants with persistent modest TSH elevation (6–20 mIU/L in serum) but normal levels of FT4. Therefore, further defining the risks and appropriate treatment of mild congenital hypothyroidism is important, but a randomized, controlled trial to resolve this issue may be difficult to

accomplish given the prevailing bias (and perhaps the ethical duty) not to withhold treatment from these infants.

Several recent studies have attempted to address this question. A series of studies in Belgian children that assessed the relationship between newborn screening TSH concentrations and various neurodevelopmental outcomes found no relationship between mild TSH elevation (up to 15 mIU/L) and cognitive or psychomotor development or parent-reported behavior scores at 4–6 years of age. However, the power of these studies to detect differences in outcomes was limited by the small number of patients with elevated TSH concentrations, particularly in the 10–15 mIU/L range.

A different conclusion was reached by an Australian study that linked newborn screening results with standardized national assessments of childhood development and school performance. This population-based analysis of over 500,000 children found that the risk of poor educational or developmental outcome rose continuously with increasing newborn screening TSH concentration from the 75th to the 99.9th percentile, even after adjusting for potential confounders. Interestingly, no increased risk was observed among infants with screening TSH levels above the 99.9th percentile (12–14 mIU/L), perhaps due to these patients being diagnosed with and treated for congenital hypothyroidism. This study has limitations, including the lack of many patient-level details (including the possibility of diagnosis and treatment of congenital hypothyroidism), inability to account for the potential confounding effect of iodine deficiency, and the inability to establish causality from the observational study design.

Despite the unresolved question of whether infants with mild congenital hypothyroidism benefit from treatment, detecting mild TSH elevations on newborn screening may have other advantages. In particular, a proportion of infants with mild TSH elevation at screening may actually have congenital hypothyroidism that requires treatment. For example, about 12% of infants confirmed to have permanent congenital hypothyroidism—including both dysgenesis and dyshormonogenesis—have only mild TSH elevation at screening. Conversely, among infants with mild initial TSH elevation, between 3% and 30% (depending on the specific cut-off used) prove to have permanent congenital hypothyroidism. In a substantial number of these patients, TSH concentrations are much higher when measured in the confirmatory serum sample than was suggested by an initial mild abnormality that would be missed by a higher TSH cut-off. This issue may be particularly significant in preterm and low birth-weight infants with congenital hypothyroidism, in whom the TSH rise may be delayed. Still, these potential advantages of lower TSH cut-offs come at the expense of increased costs of screening, increased parental anxiety over abnormal results of uncertain significance, and the potential for overtreatment with levothyroxine, which itself may be associated with adverse neurodevelopmental outcomes. [11, Rank 1]

**Primary Hypothyroidism**

Primary hypothyroidism or thyroid hormone deficiency due to abnormality in the thyroid gland is the most common endocrine disease. The prevalence of hypothyroidism in the general population ranges from 3.8%–4.6%. The Whickham survey showed an annual incidence of hypothyroidism of 4.1 per 1000 in women and 0.6 per 1000 in men. Furthermore, a more recent study from the UK suggests that the incidence of hypothyroidism is rising, although there appears to be geographical variation. In the UK, over 23 million prescriptions for levothyroxine were written in 2010, making it the third most prescribed medication after simvastatin and aspirin.

Diagnosis and treatment of hypothyroidism is often considered simple and is mostly carried out in a primary care setting. However, studies continue to show problems in the management of this condition. Many patients on thyroid hormone replacement are either under-replaced or over-replaced and a significant number of patients on thyroid hormone replacement report not feeling well despite having thyroid function tests within the healthy reference range.

The common clinical features associated with hypothyroidism are tiredness, weight gain, dry skin, cold intolerance, constipation, muscle weakness, puffiness around the eyes, hoarse voice, and poor memory. However, a study surveying thyroid disease in Colorado has shown that the sensitivity of individual symptoms ranges from 2.9% to 24.5%. Although the likelihood of hypothyroidism increases with increasing numbers of symptoms, absence of symptoms does not exclude the diagnosis. Furthermore, these symptoms are non-specific and common in the euthyroid population with around 20% of euthyroid subjects having four or more hypothyroid symptoms. Therefore, the diagnosis of hypothyroidism must be made biochemically.

Overt primary hypothyroidism is diagnosed biochemically with a serum thyroid stimulating hormone (TSH) concentration above the reference range and low free T4. If the TSH is raised but free T4 is in the normal range then this is referred to as subclinical hypothyroidism. The population reference range of TSH is around 0.4–4.5 mIU/L and most patients with overt hypothyroidism have TSH above 10 mIU/L. However, several controversies surrounding the TSH reference range have surfaced in recent years. Firstly, because the TSH in the general population is not normally distributed, and more than 95% of healthy individuals have TSH less than 2.5 mIU/L, it has been suggested that the upper limit of the TSH reference range may be skewed by occult thyroid dysfunction, leading to a debate whether the upper limit of the TSH reference range should be lowered from 4.5 to 2.5 mIU/L. Secondly, in pregnancy, it is now recognized that trimester-specific reference ranges for TSH should be used to assess thyroid function; when trimester-specific reference ranges are not available, TSH of 2.5 mIU/L in the first trimester and 3 mIU/L in the later trimesters are considered as the upper limits of the reference range. Thirdly, because the TSH distribution and reference limits are influenced by age and ethnicity, the use of age and race-standardized TSH reference ranges has also been suggested. Finally, it has been shown that variation of TSH within an individual is narrower than the variation in the general population, supporting the

concept of an individual reference range, such that a TSH level within the population reference range may still be abnormal for the individual. It is thought that genetic factors play a part in influencing the thyroid set-point in the individual. This is supported by studies showing associations between TSH and common variations in different genes, including *PDE8B* and *TSHR*, and a study showing that a common variation in the *PDE8B* gene influences TSH reference ranges in pregnant women. [12, Rank 3]

**Triiodothyronine-levothyroxine combination therapy**

A significant minority of hypothyroid patients treated with levothyroxine do not feel completely well and have a poorer quality of life. There are several possible causes for impaired wellbeing in these patients. Firstly, a number of them have a TSH outside the normal range, suggesting a suboptimal dosage of levothyroxine. Secondly, given that both hypothyroidism and dysphoria are common diagnoses, there will be a clinical overlap and thus symptoms attributed to hypothyroidism may not improve with treatment. Moreover, patients feeling unwell are more likely to seek medical advice and thus get their thyroid function tested. Thirdly, decreased wellbeing could be due to intrinsic autoimmunity irrespective of the patient's thyroid status. Lastly, serum TSH may not accurately reflect thyroid hormone concentrations in all target tissues. In a community-based survey, patients on levothyroxine, despite having normal TSH, were found to have significantly reduced psychological wellbeing as compared with age-matched and gender-matched controls. Likewise, a cohort study showed poorer quality of life and decreased neurocognitive functioning in 141 hypothyroid patients on adequate doses of levothyroxine as compared with the general population. Indeed, many patients on levothyroxine do not achieve a physiological Free T3/Free T4 (FT3/FT4) ratio despite serum TSH being within the reference range, suggesting that hepatic and renal conversion of thyroxine to triiodothyronine may be impaired in these patients and this may account for the persistence of their symptoms. Furthermore, in thyroidectomized rats, tissue euthyroidism could be achieved by infusion of both levothyroxine and triiodothyronine and not by levothyroxine alone. A triiodothyronine-levothyroxine combination is necessary to restore tissue euthyroidism in patients with hypothyroidism.

Several studies have evaluated triiodothyronine-levothyroxine combination therapy in patients with hypothyroidism. An early study from Lithuania showed significant improvement in wellbeing when 50 μg of levothyroxine was replaced with 12.5 μg of triiodothyronine; however, several subsequent randomized controlled trials have failed to confirm this effect. A meta-analysis of eleven randomized controlled trials involving 1216 patients concluded that a triiodothyronine-levothyroxine combination is not more effective than levothyroxine alone. Interestingly, patients in two trials reported a preference for combination therapy despite no objective improvement in wellbeing. A major limitation of these studies is that triiodothyronine in the current formulation does not result in a normal physiological profile and the triiodothyronine-levothyroxine combination has been shown to

be associated with wide fluctuations in FT3 levels. Furthermore, it is possible that combination therapy is effective only in a subgroup of patients. This is supported by a recent study, which showed that a common genetic variation in the deiodinase type 2 (*DIO2*) gene is associated with worse baseline quality of life scores in hypothyroid patients on levothyroxine and greater response to the combination therapy. [13, Rank 5]

**Levothyroxine Replacement in Special Circumstances**

Subclinical Hypothyroidism

Although subclinical hypothyroidism is a biochemical diagnosis characterized by raised TSH with normal serum thyroid hormone levels, many patients have nonspecific symptoms. Subclinical hypothyroidism is common in the general population (with a prevalence of 4%–8%) and the prevalence increases with advancing age. It can progress to overt hypothyroidism; the 20-year follow-up study of the Whickham survey has shown that 4.3% people with raised TSH and positive thyroid antibodies and 3% with raised TSH without antibodies develop overt hypothyroidism annually. However, a prospective study has shown that, in about 5% of patients with subclinical hypothyroidism, TSH returns to normal after 1 year without any treatment. Likewise, in another large study, 51% of 3775 patients with TSH 5.5–10 mIU/L were found to have TSH levels within the reference range when tested 5 years later. Observational studies have shown inconsistent associations between subclinical hypothyroidism and hyperlipidemia, endothelial dysfunction, cardiovascular disease, and cognitive impairment. A recent meta-analysis of individual data for over 55,000 subjects from eleven studies showed that subclinical hypothyroidism is associated with an increased risk of cardiovascular events and mortality, particularly if TSH is 10 mIU/L or higher. Although randomized controlled trials have shown a trend towards improved lipid profile, endothelial function, and echocardiographic features with levothyroxine treatment in patients with subclinical hypothyroidism, there are no studies to show that levothyroxine reduces cardiovascular events or mortality. Furthermore, a recent randomized controlled trial showed no evidence of improvement of cognitive function with levothyroxine treatment in elderly patients with subclinical hypothyroidism.

Routine use of levothyroxine in subclinical hypothyroidism is controversial. An expert panel has supported the use of levothyroxine in patients with subclinical hypothyroidism if TSH is higher than 10 mIU/L. While subclinical hypothyroidism in pregnant women and women planning to conceive should also be treated with levothyroxine, great caution should be exercised when treating elderly patients with this condition (see below). In symptomatic patients with subclinical hypothyroidism and TSH below 10 mIU/L, a 3–6-month trial of levothyroxine is reasonable. In asymptomatic patients with TSH less than 10 mIU/L, TSH should be monitored annually in the presence of thyroid antibodies and every 3 years if thyroid antibodies are absent. [14, Rank 2]

Pregnancy

Thyroid hormones are essential for the neurological development of the fetus. Because the fetal thyroid gland starts functioning only after 12–14 weeks of gestation, the fetus relies on maternal thyroid hormones for its early neurological development. Both overt and mild thyroid hormone insufficiency in pregnancy has been shown to be associated with impaired neuropsychological development of the offspring. Furthermore, maternal hypothyroidism is also associated with several other adverse obstetric outcomes, including miscarriage, premature birth, gestational hypertension, and low birth weight and these adverse events may be prevented by optimum thyroid hormone replacement.

Maternal hypothyroidism diagnosed in pregnancy should be corrected as soon as possible by initiating a full replacement dose of levothyroxine (100–150 μg/day or 2.0–2.4 μg/kg body weight/day). Most women with known hypothyroidism need a 30%–50% increase in the dose of levothyroxine during pregnancy and this increased dose requirement occurs as early as the first 4–6 weeks of gestation. About a quarter of pregnant hypothyroid women on levothyroxine have high TSH, suggesting under-replacement at their first antenatal visit. This could, to some extent, be prevented by preconception optimization of levothyroxine dose and, for hypothyroid women planning pregnancy, levothyroxine dose ideally should be adjusted to keep TSH less than 2.5 mIU/L before conception. Thyroid function should be checked as soon as the pregnancy is confirmed to adjust the dose of levothyroxine further. An alternative approach is to advise the woman to increase the dose of levothyroxine by 30%–50% or by two tablets per week as soon as pregnancy is confirmed to avoid any delay in dose increment. Thyroid function should be monitored at regular intervals (every 4–6 weeks) to adjust the dose of levothyroxine to keep TSH under 2.5 mIU/L in the first trimester and under 3.0 mIU/L in the second and third trimesters.

There is general consensus that subclinical hypothyroidism in pregnant women should also be treated with levothyroxine. However, whether all pregnant women should be screened for subclinical hypothyroidism remains controversial. [15, Rank 4]

Elderly

The levothyroxine dose requirement gradually decreases with age, thought to be due to age-related decreases in thyroxine degradation and in lean body mass. Furthermore, levothyroxine replacement may precipitate severe angina or myocardial infarction in an elderly person with asymptomatic ischemic heart disease. Therefore, in people over the age of 65 years, levothyroxine should be started at a small dose (25–50 μg/daily) and dose titration should be carried out slowly.

There is a high prevalence of suboptimal thyroid hormone replacement in the elderly. In a cross-sectional study involving elderly people aged 65 years or over on levothyroxine, 41% and 16% had suppressed and raised TSH suggestive of over-replacement and under-replacement, respectively. The risk of under-replacement of levothyroxine is less certain in this population, with studies showing an association between raised TSH and a lower

mortality rate in the very elderly population. In contrast, the potential hazards of over-replacement of levothyroxine in the elderly population have been highlighted by the associations between suppressed TSH with reduced bone mineral density as well as increased risk of fractures. In a recent large cohort study of elderly people above the age of 70 years, levothyroxine treatment has been found to be associated with an increased risk of fractures. Although thyroid function tests were not analyzed in this study, there was a correlation between the risk of fractures and the dose of levothyroxine, suggesting that the increased fracture risk may be related to over-replacement of levothyroxine. Several epidemiological studies have also shown an association between low or suppressed TSH and atrial fibrillation. However, all of these studies, except the Framingham study, have excluded patients on levothyroxine and, therefore, it remains unclear whether suppressed TSH due to exogenous levothyroxine is as deleterious to the heart as endogenous subclinical hyperthyroidism.

Ischemic heart disease

Prolonged untreated hypothyroidism can lead to persistent bradycardia, an adverse atherogenic lipid profile, and deterioration in myocardial function. However, due to the positive inotropic and chronotropic effects of thyroid hormone on the heart, starting a full dose of levothyroxine could precipitate acute coronary syndrome in hypothyroid patients with previously silent coronary artery stenosis. Therefore, newly diagnosed hypothyroid patients with ischemic heart disease should be started on a small dose of levothyroxine (12.5–25 μg/day) which is slowly up titrated every 4–6 weeks in increments of 12.5–25 μg/day until euthyroidism is achieved. Some patients may need to increase their antianginal medications to ensure full beta-blockade, or undergo a coronary revascularization procedure to be able to tolerate an adequate dose of levothyroxine to achieve euthyroidism. [16, Rank 1]

Poor compliance

In a subset of hypothyroid patients in whom poor compliance with daily dosing of levothyroxine is suspected, a onceweekly dosage of levothyroxine may be used as an alternative. In a randomized crossover trial involving 12 hypothyroid patients, once-weekly administration of seven times the normal daily dose of levothyroxine was shown to be effective and well tolerated. The study found a higher mean TSH level when patients were on a weekly regime compared with daily dosing, suggesting that a dose slightly higher than the calculated 7 day total may be needed to achieve optimum biochemical control on weekly regime. Because a high dose of levothyroxine may exacerbate angina or precipitate myocardial infarction, the weekly regime of levothyroxine is not appropriate for patients with ischemic heart disease. Furthermore, because the long-term adverse effects of a weekly levothyroxine regime are not known, it should be used only in exceptional cases of noncompliance after other approaches have failed.

**Biochemically euthyroid patients with symptoms of hypothyroidism**

Because symptoms of hypothyroidism are nonspecific, many patients have such symptoms without biochemical evidence of hypothyroidism. A randomized, double-blind, placebo-controlled, crossover trial involving 25 patients with symptoms of hypothyroidism but normal biochemistry showed no benefit from levothyroxine in improving wellbeing and cognitive function. Given that levothyroxine is an ineffective treatment and is associated with some adverse outcomes, it should not be used in these patients. [17, Rank 2]

**Association Between Hypothyroidism and Mortality in Dialysis Patients**

In nondialysis populations with high underlying cardiovascular risk, hypothyroidism is associated with greater cardiovascular and all-cause mortality. The exaggerated cardiovascular risk inherent to ESRD suggests that dialysis patients might be particularly vulnerable to the ill effects of hypothyroidism. Existing data in CKD/ESRD patients show that hypothyroidism is associated with surrogate cardiovascular outcomes, such as ventricular dysfunction and hypertrophy, atherosclerosis, and endothelial dysfunction. Some studies have considered hard outcomes, showing that lower (total/free) T3 and/or thyroxine (T4) levels are associated with all-cause and cardiovascular mortality in dialysis populations.

However, T3/T4 levels are particularly prone to deviations on the basis of nonthyroidal illness and thus, may not accurately reflect thyroid functional status. For example, peripheral conversion of T4 to T3 by types I and II deiodinase (the source of 80% of T3) is sensitive to health status, cytokines, cortisol, medications, and uremia. Additionally, uremic toxins as well as low albumin states interfere with *in vitro* FT4 assays, rendering observed measures lower than actual circulating levels. For these reasons, studies using T4/T3 to define thyroid function are subject to confounding, and serum TSH is considered to be a more specific thyroid functional status metric. Moreover, owing to the logarithmic T3/T4 and TSH relationship (*i.e.*, minimal T3/T4 changes induce large reciprocal TSH changes), TSH is a more sensitive marker of hypothyroidism, and it is more robust to measurement error. Although the clearance, diurnal pulsatility, response to thyrotropin releasing hormone, and half-life of TSH may be altered in renal failure, most CKD/ESRD patients have normal TSH levels and respond appropriately to changes in circulating levels of thyroid hormone (*i.e.*, TSH levels decrease and rise in response to exogenous T3 and thyroid ablation, respectively). Furthermore, metabolic testing in ESRD patients has shown that TSH is a more reliable indicator of thyroid functional status than T3.

Several of the above studies evaluating hypothyroidism and mortality in ESRD patients have indirectly examined for - and not detected - associations between TSH levels and mortality. However, none contained a sufficient number of patients with actual hypothyroidism (*i.e.*, elevated TSH), in instances caused by exclusionary restriction, to be powered in this regard. Instead, studies compared TSH deviations within the normal range. This study is, therefore, the first to show an association between hypothyroidism *per se* and mortality in the ESRD

population. Because of data limitations, they were unable to directly examine the association between hypothyroidism and cause-specific mortality.

However, they performed sensitivity analyses in which they adjusted for cardiovascular risk factors and observed dramatic attenuation of the hypothyroidism–mortality association. There are two potential explanations for this observation. (*1*) Cardiovascular illness is one means by which hypothyroidism increases mortality (*i.e.*, hypothyroidism→cardiovascular morbidity→death); under this logic, the true impact of hypothyroidism on survival is better represented by estimates that are not adjusted for cardiovascular comorbidity. (*2*) Cardiovascular disease is a confounder of the association between hypothyroidism and death (*i.e.*, cardiovascular disease→hypothyroidism→death); under this logic, the true impact of hypothyroidism on survival is better represented by estimates that are adjusted for cardiovascular comorbidity. Empirical distinction between these two explanations is not possible, and interpretation must, therefore, be guided by content area logic. Researchers favor the former interpretation, because whereas there is abundant data indicating that hypothyroidism induces cardiovascular disease (*e.g.*, alterations in myocyte contractility/relaxation, flow-mediated vasodilation, and arterial stiffness that distort ventricular geometry and function; cardiac channel expression changes that prolong the cardiac action potential and QT interval and increase Torsades risk; hyperhomocysteinemia; coagulation and fibrinolysis alterations; and systemic vascular resistance and lipid derangements accelerating atherogenesis), they are not aware of data suggesting that cardiovascular disease causes hypothyroidism. However, given data limitations, they were not able to assess the temporal sequence of TSH measurement versus comorbid cardiovascular event incidence, and therefore, they could not formally distinguish whether cardiovascular morbidities were confounders or pathway intermediates. [19, Rank 2]

**Future Perspectives**

After more than 120 years since first successfully treated hypothyroidism with sheep thyroid extract and numerous subsequent advances in the field, there remain many uncertainties surrounding the management of this common disease. Furthermore, although there is increasing evidence from observational studies for an association between subclinical hypothyroidism and the risk of cardiovascular disease-related morbidity and mortality, randomized controlled trial evidence showing that levothyroxine treatment reduces the risk is still lacking. Interestingly, subclinical hypothyroidism can be viewed as an incipient autoimmune disease that develops into overt hypothyroidism over many years. Identification of biomarkers that are better than current thyroid antibody assays at predicting eventual hypothyroidism could lead to targeted intervention to prevent hypothyroidism. Oral selenium supplementation appears to have efficacy in modifying the natural history of Graves' orbitopathy, and may prove to have immunomodulatory actions in other forms of autoimmune thyroid disease. In pregnancy, results of ongoing and future clinical trials are awaited to inform whether all pregnant women should be screened and treated for subclinical hypothyroidism.

It remains uncertain as to why a minority of hypothyroid patients on levothyroxine continue to have residual symptoms despite apparently adequate replacement, and it is hoped that future studies will clarify this enigma. Moreover, despite several randomized controlled trials showing a lack of benefit of combining triiodothyronine with levothyroxine in such patients, it is possible that triiodothyronine formulated to mimic the normal physiological profile may have a better outcome. Indeed, a proof of concept study has demonstrated the biochemical efficacy of a combination of long-acting triiodothyronine and levothyroxine on the T4/T3 ratio and TSH over levothyroxine monotherapy. [18, Rank 5]

**Conclusion**

It is clear that thyroid hormones play a significant role in regulating cardiac, vascular, and metabolic physiology. Physiologic alterations from both overt and subclinical hypothyroidism have varied cardiovascular effects, and treatment may reverse some, if not all, of the effects. There is evidence to suggest that treatment of mild dysfunction can improve cardiovascular outcomes; however, randomized controlled clinical trials in this field are lacking and warranted. It is important to note that TSH levels can be higher in older populations but may not necessitate treatment, and treatment initiated in the elderly should be gradually escalated with close monitoring. [20, Rank 4]

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