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CME CREDIT HOURS

Clinical implications of the interaction between hypothyroidism and the cardiovascular system

KEY POINTS:

Hypothyroidism does not usually cause congestive heart failure, unless there is underlying heart disease.

Treat hypothyroidism in patients with possible coronary artery disease very cautiously, because thyroid hormone replacement can precipitate or aggravate angina.

In hypothyroid patients with stable angina, begin with low doses of thyroid hormone and increase the dose to physiologic levels as tolerated.

Stabilize unstable angina before initiating thyroid hormone replacement.

Screen all patients with high cholesterol levels for hypothyroidism.

ABSTRACT: Hypothyroidism frequently causes cardiovascular manifestations that can complicate treatment of both the hypothyroidism and of any underlying heart disease. This review discusses mechanisms, pathophysiology, and management.

Although "myxedema heart" was first described a century ago,[1] and its characteristic features of the dilated cardiac silhouette, low electrocardiographic voltage with virtual absence of P and T waves, and slow indolent heart action were described in 1914,[2] patients today very rarely present with these full-blown, classic features. Rather, thanks to earlier diagnosis, most patients present with nonspecific signs and symptoms such as fatigue, cold intolerance, and weight gain (**TABLE 1**). In fact, a marked degree of hypothyroidism must be present for at least several months before cardiac manifestations such as bradycardia and low cardiac output become apparent.

Although thyroid hormone replacement can reverse many of the cardiovascular effects of hypothyroidism, care must be taken that treatment does not complicate underlying heart disease.

HOW HYPOTHYROIDISM AFFECTS THE HEART

Hypothyroidism affects the heart both indirectly (through its effects on the metabolic pathways) and directly.[3,4]

Indirect effects

Low blood volume, vasoconstriction. Hypothyroidism causes decreased metabolism, which reduces peripheral oxygen demand. This in turn causes diminished production of erythropoietin and

TABLE 1

HYPOTHYROIDISM: SIGNS AND SYMPTOMS

Cold intolerance
Constipation
Lethargy and fatigue
Weight gain
Abnormal menstrual periods
Coarsening of hair
Dry, scaly skin, brittle nails
Bradycardia
Hypertension
Elevated cholesterol

consequently lower red cell mass and vascular volume. In addition, there is decreased formation of some of the metabolic end products that mediate local vasodilatation, resulting in increased systemic vascular resistance and increased diastolic blood pressure.

Direct effects

Decreased adrenergic stimulation. Hypothyroidism affects the heart directly by decreasing the number of beta receptors. This effect may explain why hypothyroid patients are less sensitive to adrenergic stimuli and are prone to bradycardia.

Decreased contractility. In addition, animal studies show that hypothyroidism alters the activity of several cardiac proteins involved in cardiac contraction, such as myosin adenosine triphosphatase (myosin ATPase) and sarcoplasmic reticulum calcium ATPase.[3,5]

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Myosin ATPase is the enzyme necessary for hydrolysis of adenosine triphosphate to adenosine diphosphate, the reaction that generates the high-energy phosphate molecule necessary for actin-myosin cross bridging. This enzyme exists in three different isoforms in the rat heart; myosin V1 is the most active form, and myosin V3 is the least. Under normal thyroid conditions, myosin V1 is the most prevalent, but in hypothyroidism there is more production of myosin V3, resulting in decreased cardiac contractility.[6]

Reduced cardiac filling. Also decreased is the activity of sarcoplasmic reticulum calcium ATPase, which is responsible for pumping cytosolic calcium into the sarcoplasmic reticulum during diastole. The result is slower relaxation during diastole and decreased force of contraction during systole, due to decreased calcium release from the sarcoplasmic reticulum.

Although similar changes in enzymatic activity occur in the human heart, their functional significance is still not known. An echocardiographic study showed that diastolic filling (as reflected by isovolumic relaxation time and the rapid thinning phase of the posterior wall) is more prolonged in hypothyroid persons without signs or symptoms of cardiovascular disease than in normal subjects. These changes normalized with thyroid hormone replacement.[7] The rapidity with which treatment can reverse these alterations in ventricular function suggests that they are related to the active part of the relaxation process and the regulation of intracellular calcium influx rather than to acute abnormalities in the architecture of the ventricle.

CLINICAL MANIFESTATIONS

Low cardiac output, but rarely congestive heart failure

All the factors listed above contribute to low cardiac output (**FIGURE**) and a prolonged circulation time.[8] Nevertheless, arteriovenous oxygen extraction is normal, indicating that the low cardiac output matches the low metabolism and oxygen consumption of the periphery.[4] Thus, myxedema in itself, without underlying heart disease, rarely leads to congestive heart failure. In addition, cardiac output does increase to a nearly normal extent in response to exercise.[9]

Nevertheless, congestive heart failure, although rare, has been reported in severely hypothyroid patients without underlying heart disease.[10,11] A case report from Japan described a middle-aged woman with myxedema who presented with congestive heart failure. No significant stenosis was observed on coronary angiography. Thyroid-replacement therapy, digitalis, and diuretics produced dramatic clinical improvement. A transvenous right ventricular endomyocardial biopsy demonstrated vacuolated degeneration, which improved after therapy except for a slight degree of fibrosis.[12]

The features of advanced myxedema such as dyspnea on exertion, easy fatiguability, and decreased exercise tolerance may be easily confused with congestive heart failure.

However, earlier studies indicate that pulmonary congestion does not usually occur in myxedema.[13] In addition, hypothyroid patients respond normally to exercise by increasing their cardiac output, whereas patients with congestive heart failure have an impaired response.[8]

Pericardial effusion

In most hypothyroid patients with an abnormal cardiac silhouette, echocardiographic studies show that the cause is pericardial effusion, not congestive heart failure.[14] Pericardial effusion usually develops gradually over a long time and is rarely complicated by cardiac tamponade.[15] Although pericardial effusion occurred in 30% to 80% of patients with myxedema in early reports, it was much less common in more recent studies (7% in one study), probably because today's patients have less severe myxedema at the time of diagnosis.[16]

Atherosclerosis

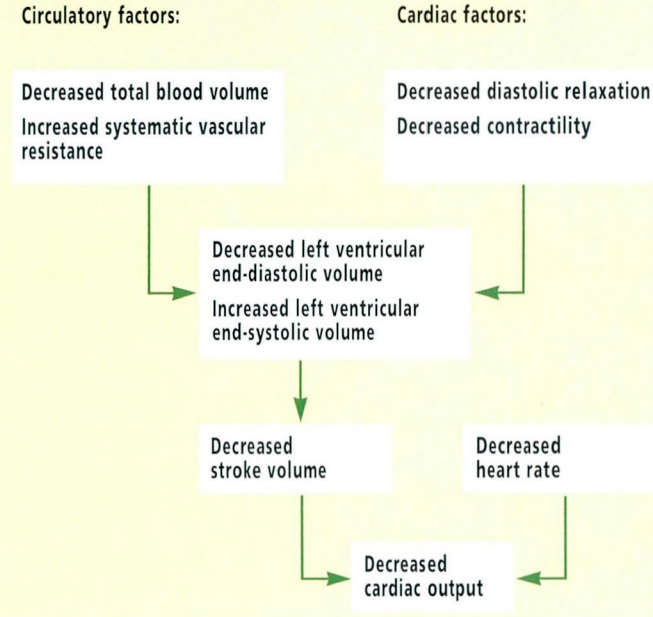
Patients with hypothyroidism may be at increased risk of developing atherosclerosis,[17] as coronary atherosclerosis is twice as common in myxedematous patients than in sex- and age-matched controls.[18] In addition, hypothyroidism enhances the development of atherosclerosis in cholesterol-fed animals, and thyroid hormone replacement reduces it.

It is unknown whether hypothyroidism per se causes this higher prevalence of atherosclerosis, or if it is related to other factors such as hyperlipidemia and hypertension, which occur more frequently in hypothyroidism. In the classic autopsy studies reported by Steinberg in 1968,[18] coronary artery disease was more prevalent in hypertensive than in normotensive myxedematous patients.[18] In addition, hypothyroid patients often have elevated homocysteine levels,[19] another risk factor for atherosclerosis.[20]

Hyperlipidemia. Hypercholesterolemia has been recognized as a clinical feature of myxedema for more than 60 years.[21] Hypothyroid patients often have increased levels of total cholesterol, LDL cholesterol, VLDL cholesterol, and HDL cholesterol[22]; the opposite effects are seen in hyperthyroidism. The prevalence of hypothyroidism in patients with hypercholesterolemia is at least two times that in the general population.[23,24] Thus, all patients with hypercholesterolemia should be screened for hypothyroidism.

FIGURE

FACTORS THAT LEAD TO DECREASED CARDIAC OUTPUT IN HYPOTHYROIDISM



Several factors explain these lipid abnormalities. Decreased expression of the LDL receptor results in decreased uptake of LDL particles by the liver.[25,26] Marked reduction in the activity of the hepatic lipase enzyme results in slightly elevated HDL-cholesterol levels, mainly the HDL2 subfraction.[27] Decreased activity of the lipoprotein lipase enzyme, which is important for clearance of VLDL particles, leads to hypertriglyceridemia,[28,29] even though production of triglyceride-rich lipoproteins is diminished in hypothyroidism.[30]

Several cross-sectional studies showed that cholesterol levels correlate well with the severity of myxedema.[31,32] In patients with markedly elevated thyroid-stimulating hormone levels, LDL cholesterol levels can be 30% to 50% above normal.

However, it is more difficult to document a relationship between thyroid status and cholesterol levels within normal or slightly depressed ranges of thyroid function than in overt hypothyroidism. Although longitudinal studies have shown that treating subclinical hypothyroidism with thyroid hormone replacement can lower LDL cholesterol levels and the LDL-HDL ratio (**TABLE 2**),[33–35] larger prospective studies are needed to clarify the long-term benefits and risks of such therapy.

Drugs used to treat angina are more likely to have adverse effects in hypothyroid patients, in part because drug metabolism is slowed

TABLE 2

EFFECTS OF TREATMENT OF MILD HYPOTHYROIDISM ON SERUM LIPIDS*

Measurement	Before thyroid treatment (n = 13)	After thyroid treatment (n = 10)
Thyroid-stimulating hormone, μU/mL	16.6 ± 3.2	3.2 ± 0.7†
Free thyroxine index	7.4 ± 0.6	9.3 ± 0.9
LDL cholesterol, mg/dL	143 ± 12	112 ± 8†
HDL cholesterol, mg/dL	46 ± 4	50 ± 4

*Data adapted from Arem and Patsch, reference 34, with permission
†Statistically different from the starting value, P < .05

Hypercholesterolemia caused by overt hypothyroidism usually improves within a few weeks of starting thyroid hormone replacement. Persistence of hypercholesterolemia after achieving euthyroid status suggests a superimposed hyperlipoproteinemia.[36]

In most hypothyroid patients with an abnormal cardiac silhouette, echocardiographic studies show that the cause is pericardial effusion, not congestive heart failure

Hypertension

A link between hypothyroidism and diastolic hypertension has been known for many years.[37,38] In a recent Japanese study of 477 female patients with chronic thyroiditis, the prevalence of hypertension in 169 hypothyroid patients was approximately three times that in 308 euthyroid patients (14.8% vs 5.5%; $P < .01$).[39]

Thyroid hormone replacement has been shown to lower blood pressure in most hypertensive hypothyroid patients. Streeten et al[40] found that induction of hypothyroidism with radioactive iodine treatment led to a significant increase in diastolic blood pressure in 16 (40%) of 40 thyrotoxic patients. Subsequent thyroid hormone replacement significantly reduced systolic and diastolic blood pressure, and the latter decreased to less than 90 mm Hg in 9 of these 16 patients.

In addition, in a survey of 688 consecutive hypertensive outpatients, 3.6% were hypothyroid, and in this subset, diastolic blood pressure decreased significantly after adequate thyroid replacement, suggesting a cause-and-effect relation.

The mechanism of hypertension in hypothyroidism remains unknown.[41] Although norepinephrine levels have been reported to be high in hypothyroid patients, adrenergic responsiveness is variable.[42,43] In some studies, there was evidence of a decrease in alpha and beta adrenergic sensitivity in hypothyroid patients,[44,45] but this was not found in other studies.[46,47] These conflicting findings may be explained in part by the differences in the severity of hypothyroidism in the study groups or differences in the methods used to assess adrenergic responsiveness.

The increased plasma norepinephrine levels in patients with severe myxedema may be part of a compensatory increase in sympathetic tone to maintain normal blood pressure in the face of decreased alpha and beta adrenergic responsiveness. Plasma renin activity, aldosterone, and angiotensin levels have also been found to be low in patients with hypothyroidism, suggesting no role for the renin-angiotensin system in this form of hypertension.[48] Finally, vasopressin may contribute to the increased peripheral resistance seen in hypothyroidism, as plasma levels have been reported to be mildly increased in hypothyroidism and to return to normal after replacement therapy.[49]

Coronary artery disease

Although coronary artery disease is more prevalent in hypothyroid patients than in euthyroid controls, the frequency of angina pectoris and myocardial infarction is not.[50] This paradox is probably due to the protective effects of hypothyroidism such as decreased myocardial oxygen demand, decreased platelet adhesiveness, and prolonged partial thromboplastin time.[51]

However, severe hypothyroidism has some deleterious effects on the ischemic myocardium. The higher systemic vascular resistance, decreased myocardial contractility, and reduced red blood cell levels of 2,3 diphosphoglycerate result in less-efficient oxygen delivery to the myocardium.[52] Further, the diminished myocardial reserve that results from hypothyroidism can worsen the consequences

of myocardial infarction.

In an experiment in dogs in which the coronary arteries were clamped, hypothyroid animals had larger infarcts, greater reductions in cardiac output and blood pressure, slower recovery, and more severe arrhythmias than did the control animals.[53]

The above observations may explain the variable effects of thyroid hormone replacement in patients with coronary artery disease.

In a retrospective study in 1961, Keating et al found that 90 of 1503 patients with hypothyroidism had coexisting angina pectoris.[54] Of these, 55 patients (60%) had pre-existing angina, and the rest (40%) developed angina only after starting thyroid hormone replacement. Angina decreased or disappeared in more than one third of patients with pre-existing angina after they started thyroid hormone therapy, whereas it worsened in nine patients (16%). In all, 11% of patients with pre-existing angina and 23% of those with new-onset angina suffered myocardial infarction during the first year of thyroid hormone replacement. Patients who developed angina after starting thyroid hormone replacement were an average of 10 years older than those who did not.

Angina management. Diagnosing coronary heart disease in myxedematous patients before starting thyroid hormone replacement can be quite difficult.[50,55] Resting and exercise electrocardiograms in these patients often show ischemic-like S-T segment and T-wave changes, which disappear with thyroid hormone replacement. In addition, cardiac enzymes may be significantly increased in the serum of hypothyroid patients because of chronic ongoing cardiac or skeletal muscle damage or decreased enzyme clearance rates.

In addition, drugs used to treat angina are more likely to have adverse effects in hypothyroid patients, in part because drug metabolism is slower.[50] The use of beta blockers is often limited by the onset of symptomatic bradycardia and, occasionally, by the onset or worsening of congestive heart failure. Hypothyroid patients are also more sensitive to nitrates, probably because of their diminished intravascular volume, resulting in a higher incidence of symptomatic postural hypotension.

In hypothyroid patients with stable angina, replacement therapy should always begin with low doses of thyroid hormone (12.5 to 25 µg of levothyroxine). The dose should then be increased in successive small increments at intervals of several weeks to achieve physiologic levels.

Unstable angina should be approached the same way in patients with hypothyroidism as in euthyroid patients. Cardiac catheterization can be done safely without hormone replacement.[55–57] In fact, since replacement therapy can worsen unstable angina and induce myocardial infarction, it should be attempted only after coronary revascularization.[54,55,58,59] Coronary artery bypass graft surgery can be performed safely in hypothyroid patients.[55] Although some studies showed a greater incidence of postoperative complications in hypothyroid patients, overall mortality rates and lengths of hospital stay did not differ significantly from those in controls.[60,61] ■

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