Review article

Hypothyroidism and cardiovascular diseases : A review

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Abstract

Increased or decreased function of thyroid hormone on the heart and vascular system causes cardiovascular derangements. Hypothyroidism is associated with impaired left ventricular (LV) diastolic function and subtle systolic dysfunction and an enhanced risk for atherosclerosis and myocardial infarction. Objective of this review was to make an update of knowledge about hypothyroidism and cardiovascular diseases. A systematic literature search of published articles relating to hypothyroidism and coronary heart disease (CHD) was conducted. Abstract, full-text, experimental studies and review articles that discussed thyroid function and its association with the development of coronary heart disease were included. The literature survey found that overt and subclinical hypothyroidism have profound effects on cardiac risk factors like pro-atherogenic lipids, C-reactive protein, homocystine and insulin resistance. These changes lead to the development of atherosclerosis, ischemic heart disease and impaired left ventricular function.

Keywords : hypothyroidism, cardiovascular disease

Introduction

Thyroid hormone has physiological effects on the cardiovascular system.[1] Many symptoms and signs recognized in patients with overt hyperthyroidism and hypothyroidism are due to the increased or reduced action of thyroid hormones on the heart and the vascular system, respectively.

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Thyroid hormone abnormalities also cause some hemodynamic derangements. In recent decades, it has emerged that subclinical thyroid dysfunction may affect the cardiovascular system, which may increase cardiovascular risk. It is becoming increasingly apparent that acute and chronic cardiovascular disease may alter thyroid hormone metabolism and contribute to cardiovascular impairment.[2] This article will provide a review of the effects of thyroid hormone in the development of coronary heart disease.

Rationale of the review

Ischaemic heart disease or atherosclerotic coronary artery disease has become global health problem of 21st century because of its high prevalence and concomitant increase in risk of morbidity and premature death. Thyroid dysfunction, not only overt thyroid hormone abnormality but even subclinical abnormality of thyroid hormone, is also a strong indicator of risk for atherosclerosis and MI. Many investigators have suggested that abnormal level of thyroid hormone may represent a cardiac risk factor. Therefore the present review was undertaken to find out the effect of hypothyroidism in development of cardiovascular diseases. So, the study will provide us the up-to-date knowledge about hypothyroidism and cardiovascular diseases. The information obtained from this review may help physician in taking decision in clinical practice.

Methods :

A systematic literature search of published articles on the association between thyroid dysfunction and coronary heart disease (CHD) was conducted. Abstract, full-text, experimental studies and review articles that discussed thyroid function and its association with the development of coronary heart disease were included.

Discussion :

Physiological aspect of thyroid hormones :

The mature thyroid gland contains numerous follicles composed of thyroid follicular cells that surround secreted colloid, a proteinaceous fluid that contains large amounts of thyroglobulin, the protein precursor of thyroid hormones.[3] The thyroid hormones are regulated by hypothalamus-anterior pituitary-thyroid gland axis through a negative feedback mechanism. Hypothalamus secrets thyrotropin releasing hormone (TRH) which stimulates thyrotrope cells of the anterior pituitary gland to produce thyroid stimulating hormone (TSH). TSH stimulates thyroid hormone synthesis and secretion. Thyroid hormones feedback negatively to inhibit TRH and TSH production. So the serum level of TSH is a sensitive and specific marker of thyroid function.[3] Under the stimulation of TSH, the thyroid cells trap iodide to join with tyrosine molecules of thyroglobulin to make mostly T_4 and some T_3 which are stored in follicular colloid within the gland. They are then released together, or some T_4 is further deiodinated to T_3 before release. This step is also under the influence of TSH.[4] T_4 is secreted from the thyroid gland in at least 20-fold excess over T_3. Both hormones circulate bound to plasma proteins. Only the free hormone is biologically available to tissues. About 80% of T_4 is metabolized by deiodination, 35% to T_3 and 45% to reverse T_3 (rT_3). The remainder is inactivated mostly by glucuronidation in the liver and secretion into bile, or to a lesser extent by sulfonation and deiodination in the liver or kidney.[5]

Triiodothyronine (T_3), the biologically active thyroid hormone, enters into the cardiomyocyte through specific transport proteins located within the cell membrane.[6] Once in the cardiomyocyte, T_3 enters the nucleus, binds to thyroid hormones receptors (TRs) and interacts with accessory transcription factors.[1,3,7] This complex binds with specific transcriptional activators (nuclear receptor α-1) or repressors (nuclear receptor α-2) depending on the nature of the regulatory elements in the target gene that, in turn, by acting as cis- or trans-regulators, modify the rate of transcription of specific target genes.[1,3,7] These specific target genes encode both structural and functional proteins.[1,8] Among various proteins expressed by transcription, the most-extensively characterized proteins are myosin heavy chains and the sarcoplasmic reticulum protein involved in the regulation of intracellular calcium handling, namely, calcium activated ATPase and its inhibitory cofactor, phospholamban.[1,8,-11]

The acute effects of thyroid dysfunction on the cardiovascular system are more readily detectable, however, the evidence on the long term effects of thyroid dysfunction on the heart and on the cardiovascular outcomes is less clear. For example, a 20-yr follow-up study of the original Whickham Survey[12] found no association between initial hypothyroidism, raised serum TSH levels, or antithyroid antibodies and the development of coronary artery disease.[12] However, the more recent Rotterdam Study[13] concluded that patients with subclinical hypothyroidism have a significantly increased prevalence of aortic atherosclerosis and myocardial infarctions.[13]

Hypothyroidism :

In the present review 'Euthyroidism' was defined as a normal TSH concentration (0.45-4.50 mU/L), 'Subclinical hypothyroidism' was defined as a TSH concentration of more than 4.50 mU/L and less than 20 mU/L with a normal FT_4 concentration and 'Overt hypothyroidism' was defined as a TSH level of 20 mU/L or more or a TSH concentration of more than 4.50 mU/L with an FT_4 concentration level below normal (<0.7 ng/dL).[14]

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. It is often the primary process in which the thyroid gland produces insufficient amounts of thyroid hormone. It can also be secondary, i.e., lack of thyroid hormone secretion due to the failure of either adequate thyrotropin (TSH) secretion from the pituitary gland or thyrotropin-releasing hormone (TRH) from the hypothalamus (secondary or tertiary hypothyroidism) found that the prevalence of hypothyroidism, diagnosed by history and blood analysis, was 2%.[12,15] The mean age of diagnosis was 57 years, and the disease was ten-fold more common in women than in men. The disease is particularly prevalent in women older than 40 years of age. Hypothyroidism is prevalent in debilitated geriatric patients of both sexes.[15] Subclinical hypothyroidism is common in the adult population, especially among women above 60 years of age.[16,17] Up to two thirds of patients have serum TSH between 5–10 mU/L and thyroid autoantibodies.[16,17] Almost half of these individuals may progress to overt thyroid failure.[12,18]

Hypothyroidism and the cardiovascular system :

The clinical presentation of overt hypothyroidism is not obvious and most patients have few symptoms and signs.[19] Bradycardia and systemic hypertension, with narrow pulse pressure and slightly increased mean arterial pressure, and some degree of exercise impairment

are the most-common findings in patients with overt hypothyroidism.[19-21]

Hypothyroidism and arrhythmia

Many patients with overt hypothyroidism have abnormal standard ECG, including QT interval lengthening and flattening or inversion of the T wave, which reflects the prolonged cardiac action potential.[19,22,23] In addition, overt hypothyroid patients are more prone to develop ventricular arrhythmias, particularly in the presence of an underlying ischemic heart disease, due to increased electrical dispersion in the myocardium[19,22] In general, resting heart rate and blood pressure are normal in SCH subjects.[24]

Hypothyroidism and dyslipidaemia

Elevated levels of total cholesterol, LDL cholesterol, and apolipoprotein B are well documented features of overt hypothyroidism.[25]

Early studies in humans with hypothyroidism demonstrated a prolonged half-life of LDL cholesterol because of decreased catabolism, an effect that was reversible with T_4 therapy.[26] Studies have also shown that hypothyroidism causes qualitative changes in circulating lipoproteins that increase their atherogenicity. Two studies have shown that LDL is more susceptible to oxidation in patients with hypothyroidism, with normalisation after restoration of the euthyroid state.[27,28] In patients with subclinical hypothyroidism, the serum concentrations of total cholesterol, non-HDL-C, remnant-like particle cholesterol, and Apo B were significantly decreased, whereas no significant changes in the serum concentrations of low-density lipoprotein cholesterol, HDL-C, triglycerides, apolipoprotein A-I, and Lp(a) were observed. Additional potentially atherogenic effects of hypothyroidism on lipid metabolism include a reversible reduction in clearance of chylomicron remnants reduced activity of cholesteryl ester transfer protein, which is involved in reverse cholesterol transport pathway and decreased activity of hepatic lipase and lipoprotein lipase.[29,30-32] Some, but not all, cross-sectional studies have demonstrated that serum levels of total cholesterol and LDL cholesterol are higher in patients with SCH than in euthyroid controls. Danese et al[33] in their meta-analysis of the effect of therapy for subclinical hypothyroidism on serum lipid levels demonstrated a mean reduction in the total cholesterol level of 0.2 mmol/L and in the LDL cholesterol level of 0.26 mmol/L.[33]

Hypothyroidism and homocysteine

Several studies have demonstrated elevated homocysteine levels in hypothyroidism, with improvement after T_4 replacement.[28,34-38] This is likely to be caused by impaired renal homocysteine clearance, although an effect of thyroid hormone on enzymes involved in folate metabolism has also been proposed.[28,38,39] The magnitude of decline in homocysteine levels after T_4 treatment is sufficient to lower cardiovascular risk, with a decrease of 2-5 µmol/L when hypothyroid patients were treated with T4 to a level suppressing the serum TSH concentration.[37,39] One study of patients with spontaneous hypothyroidism showed a decrease of 4.6 µmol/L on restoring the euthyroid state.[28] In contrast, there are now considerable data showing that subclinical hypothyroidism is not associated with hyperhomocysteinaemia. Three case-control studies have reported no difference in homocysteine levels between individuals with subclinical hypothyroidism and euthyroid controls. Furthermore, Christ-Crain et al[36] found no significant change in homocysteine levels after treatment of subclinical hypothyroidism.[36,40,41]

Hypothyroidism and C-reactive protein (CRP),

C-reactive protein (CRP), another cardiovascular risk factor, has also been studied in relation to hypothyroidism. Christ-Crain et al.[36] measured CRP in 61 overtly hypothyroid and 63 subclinically hypothyroid patients and compared them with 40 euthyroid control subjects. CRP levels were significantly higher in both hypothyroid groups, compared with controls. However, CRP levels did not decrease with T_4 treatment of the subclinically hypothyroid patients.

Hypothyroidism and insulin resistance

Bakker et al.[42] postulated that relatively lower thyroid hormone levels might amplify the increased cardiovascular risk associated with insulin resistance.[42] Their study confirmed that insulin resistant subjects with high normal TSH levels had higher LDL cholesterol concentrations, whereas among insulin-sensitive individuals, TSH concentration was not associated with any difference in LDL level.

Hypothyroidism and atherosclerosis

An autopsy finding of diffuse atherosclerosis in a 58-yr old woman was published to William Ord's classical description of the syndrome of myxoedema.[43] Vanhaelst et al.[44] found a greater prevalence and severity of coronary atherosclerosis in the hypothyroid patients.[44] Steinberg[45] in 1968 found that women with myxoedema had more severe coronary artery disease on autopsy than did age matched women without myxoedema.[45] The association between hypothyroidism and atherosclerosis has also been shown in living patients. A study of patients undergoing coronary angiography demonstrated that those who had inadequate therapy for hypothyroidism were more likely to have angiographic progression of coronary artery disease than those with adequate replacement.[46] In a hospital-based study, men and women

with a TSH level of 4.0 mU/L or greater had higher prevalence of coronary artery disease than age matched controls (48% vs. 38% for men and 37% vs. 20% for women), although this was statistically significant only for women.[47] Conflicting data exist regarding the effect of hypothyroidism on coagulation.

Both increased and decreased platelet adhesiveness have been reported in hypothyroidism.[48,49] The degree of hypothyroidism may determine its ultimate effects on coagulation parameters.[50] These suggest a greater risk for thrombosis, which could precipitate myocardial infarction, in moderate hypothyroidism, and a bleeding tendency in severe hypothyroidism.[51] Whether SCH is an independent risk factor for cardiovascular disease is controversial.[14] Recently, a strong association between SCH and atherosclerotic cardiovascular disease, independent of the traditional risk factors (i.e., hypercholesterolemia, hypertension, smoking, diabetes mellitus), was noted in a large cross-sectional survey of postmenopausal women (the Rotterdam Study).[13]

Hypothyroidism and hypertension

The prevalence of systemic hypertension is nearly three-fold higher in patients with overt hyperthyroidism than in euthyroid subjects.[52,53] Two factors contribute to systemic hypertension in overt hypothyroidism. The first, and certainly the most-widely recognized, is the remarkable increase in peripheral vascular resistance.[19] The second, and more recently documented, is the increase in arterial stiffness, which likely results from myxedema of the arterial wall.[54,55] In general, systemic hypertension associated with overt hypothyroidism is poorly controlled by conventional treatments, whereas it promptly improves with achievement of euthyroidism.[54] This finding would encourage the routine assessment of thyroid function in all patients with preexisting systemic hypertension that becomes resistant to pharmacological treatment.[56] Significant hypofunctional abnormalities in the parasympathetic nervous system and an increased prevalence of systemic hypertension have been reported in patients with SCH.[21]

Hypothyroidism and LV function

The most-consistent cardiac abnormality recognized in patients with overt hypothyroidism is impairment of LV diastolic function, which is characterized by slowed myocardial relaxation and impaired early ventricular filling.[57,58] LV systolic function usually is only marginally subnormal, as demonstrated by slightly reduced values of ejection fraction and stroke volume filling.[57,58] On the one hand, the reduced cardiac preload, in combination with bradycardia and slightly depressed myocardial contractility, accounts for a subnormal cardiac output in overt hypothyroidism.[57,58] On the other hand, the lower cardiac performance and the abnormalities in peripheral and proximal vascular function may contribute to the poor exercise tolerance in overt hypothyroidism.[20]

Conclusion

The present review revealed that though there is controversy, overt and subclinical hypothyroidism have profound effects on non-traditional cardiac risk factors like pro-atherogenic lipids, C-reactive protein, homocystine and insulin resistance. These changes, along with traditional risk factors, lead to the development of atherosclerosis, ischemic heart disease and impaired left ventricular function.

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