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Guidelines for the Management of Dyslipidemia and Thyroid Dysfunction

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A Clinical Practice Guideline

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Chairperson

Dr. R V Jayakumar, Prof of Endocrinology, AIMS, Cochin

Core committee members

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- Dr. D Maji, HOD of Endocrinology, Vivekananda Institute of Medical Sciences, Kolkata
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- Dr. Banshi Saboo, Director-Diacare, Ahmedabad
- Dr. Sandhya Kamath, Dean-Sion Hospital, Mumbai
- Dr. Ashok Seth, Director-Cardiology, Escort Heart Center, New Delhi

Method of development

A national task force was created, under the auspices of The Indian Thyroid Society, to review the available evidences in the field and develop evidence-based guidelines. Members of the task force included highly reputed and experienced endocrinologists and gynaecologists.

This task force worked for a period of 6 months and reviewed most evidences available on the topic. They had multiple phone conversations and a meeting to evaluate the evidence and accordingly develop recommendations. Upon completion of the guidelines, it will be reviewed and approved by all of the participants as well as the extending committee.

The committee evaluated recommendations and evidence using the methodology of the United States Preventive Service Task Force (USPSTF), on the basis of the strength of evidence and magnitude of net benefit (benefits minus harms),is as follows (treatments or medical advice are referred to as a "service."):

Level of evidence	Description
Level A	Data derived from multiple randomized trials or meta-analyses
Level B	Data derived from a single randomized trials or large non-randomized trial
Level C	Consensus of opinion from experts or small studies, retrospective studies or registries
Level D	Data derived from Clinical experience

Class of recommendations	
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful or effective. It is recommended
Class IIa	Evidence is in favor of efficacy/usefulness and should be considered
Class IIb	Efficacy/usefulness is less well established and recommendation may be considered
Class III	Evidence and/or general agreement that a given treatment or procedure is not beneficial, useful or effective and in some cases may cause harm. Not recommended

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Elsevier Pharmaceutical Communications Division (South Asia)

Ajay Pratap Singh
Director

Jyotishman Boruah
Chief Coordinator and Manager Customer Relations

Dr. Pranab Sakhare
Medical Content Manager

Introduction

Cardiovascular diseases (CVD) are the most common cause of morbidity and mortality worldwide and South Asians seem to have the highest rates of coronary artery disease (CAD).[1]

According to National Commission on Macroeconomics and Health (NCMH), a government of India undertaking, there would be around 62 million patients of CAD by 2015 in India and of these 23 million would be patients younger than 40 years of age.[2]

Also the World Health Organization (WHO) has estimated that by 2020, CVD will be the largest cause of disability and death in India, with 2.6 million Indians predicted to die due to CVD.[3]

According to Enas et al the prevalence of coronary heart disease (CHD) in Asian Indians is approximately 4 times higher compared to the general population in the United States.[4]

The commonest underlying cause of CAD is atherosclerosis for which dyslipidemia has been identified as one of the major risk factor.[2,5-9]

Dyslipidemia refers to elevation of plasma cholesterol, triglycerides (TGs), or both, or a low level of high-density lipoprotein (HDL) that contributes to the development of atherosclerosis, a precursor for ischemic heart disease (IHD).[10,11]

Atherogenic dyslipidemia is characterized by three lipid abnormalities: elevated serum TG, elevated small low-density lipoprotein (sdLDL) particles, and reduced serum HDL cholesterol.[6,12]

The prevalence of dyslipidemia has shown varied results in different Indian studies. Some of the data are shown below:[2, 13-18]

	Sex of Patients in the study	Hypercholesterolemia (%)	Hypertriglyceridemia (%)	Low HDL (%)
Estari et al	Males	38.4	45.1	7.7
	Females	37	27.9	1.5
Sawant et al	Males	38.6	42.6	64.2
	Females	23.3	17.2	33.8
Reddy et al	Both males & females	37.5	24.3	-
Kumar et al	Both males & females	-	23.75	-

Kasliwal et al	Males	-	36.0	71.7
	Females	-	44.6	78.6
Sawant et al	Males	36.0	43.0	59.0
	Females	46.0	33.5	30.0
Misra et al	Males	26.8	16.8	15.8
	Females	27.5	12.3	16.7

The Indian Council of Medical Research project reported a prevalence of dyslipidemia of 37.5% among adults between age group of 15 to 64 years, with an even higher prevalence of dyslipidemia (62%) among young male industrial workers.[19]

The common pattern of dyslipidemia seen in Asian Indians is different when compared to the lipid profile of White Americans (Table 1).[4]

Table 1. Pattern of dyslipidemia among Asian Indians compared to White Americans

Lipid	Relative Serum Concentrations
TC	Similar
LDL	Similar
Small Dense LDL	Similar
TG	Higher
HDL	Lower
Lp(a)	Higher

In addition, Asian Indians tend to be physically more inactive (particularly children and young adults) and have excess truncal fat and increased intra-abdominal fat accumulation. Majority of them consume diets rich in carbohydrate and low in ω-3 polyunsaturated fatty acids. All these factors are linked to insulin resistance, hypertriglyceridemia and consequent atherogenic dyslipidemia. Moreover higher prevalence, earlier onset and increased complications of Type 2 diabetes and CHD are often seen at lower levels of body mass index (BMI) and waist circumference (WC) in South Asians than White Caucasians.[20,21,22]

High TG and low HDL cholesterol levels alone have been shown to boost the risk of cardiovascular events, independent of conventional risk factors identified in large cohort studies.[23-25]

Studies conducted by Kumar et al and Das et al have reported that apolipoprotein E polymorphisms (particularly apo E4 allele variation) have been

considered as an independent risk factor for dyslipidemia, particularly associated with low HDL-C and high TC: HDL-C ratio, and also for premature myocardial infarction (MI) in Asian Indians.[26,27]

Recommendations

- Dyslipidemia is a major risk factor for development of atherosclerosis and coronary artery disease (I/A).
- Atherogenic dyslipidemia is characterized by elevated serum TG, small dense LDL particles, and reduced serum high-density lipoprotein cholesterol (IIa/B).
- Asians are inherently prone to have atherogenic dyslipidemia, elevated Lp(a) levels, increased incidence of metabolic syndrome (MetS) and diabetes mellitus (DM) and hence early cardiovascular event (IIa/B).

Dyslipidemia and Cardiovascular Risk

The relationship between high serum total and LDL cholesterol as important risk factors for CAD development are well known.[28-32]

The composition of particles within a particular class may differ significantly. In the case of LDL particles, some are larger and more buoyant (LDL A), whereas others are smaller and denser (LDL B). The LDL A particles contain more cholesterol ester per particle than do the LDL B particles. When a TG from very low density lipoprotein (VLDL) is exchanged for a cholesterol ester in LDL by the action of the enzyme cholesterol ester transfer protein (CETP), the VLDL becomes enriched in cholesterol ester, and LDL becomes enriched in TG. Further, the TG in LDL is hydrolyzed by lipoprotein lipase or hepatic lipase resulting in a smaller and denser LDL particle. Thus, increased VLDL secretion results in increased generation of sdLDL particles, which is more likely when serum TG concentrations are >133mg/dL.

High levels of sdLDL promote atherogenesis by the following mechanisms:[22]

a) Rapid infiltration of sdLDL into the arterial wall than normal-sized LDL

b) Increased susceptibility to retention in the extracellular matrix and

c) Increased oxidation

In Asians, LDL particle size tends to be smaller and denser, thereby promoting atherogenesis.[33,34]

Several cross-sectional studies have reported that the odds of finding CAD among individuals with sdLDL particles were increased compared with those having larger, buoyant LDL particles.[35-37]

The Framingham Offspring Study reported that despite 4-fold greater cholesterol-lowering therapy use, increased LDL-C and sdLDL-C were found in 10.4% and 22.0% of men and in 24.3% and 27.8% of women with CHD, respectively. These findings may explain some of the high residual risk of future CHD events in these patients.[38]

In a study conducted by Gardener et al, incident CAD cases had significantly high sdLDL peak particle size compared with controls matched for age, sex and ethnicity.[39]

Results from the Quebec Cardiovascular Study revealed that patients with sdLDL (LDL peak particle diameter ≤25.64 nm) were associated a with

significant 3.6-fold increase in the risk of IHD. Furthermore, patients with sdLDL particles who develop IHD over a 5-year follow-up period was significantly higher than that in controls matched for age, body mass index, alcohol intake and smoking.[40]

Kulkarni et al reported that the prevalence of sdLDL type was significantly increased in Asian Indians (48% men and 41% women) who are generally characterized by the atherogenic lipoprotein profile (i.e., lower HDL-C and higher TG), compared with the age- and gender-matched White subjects (30% and 11%, respectively).[33]

Mulukutla et al studied the relationship between race and atherogenic dyslipidemia among Whites, Blacks, and Asian Indians. The prevalence of sdLDL (pattern B) and of TG/HDL ratio >3 was greatest among Asian Indians and smallest among Blacks. Compared to Whites, the adjusted odds for Indians having a LDL pattern B was 2.06 ($P < .001$) and TG/HDL ratio >3 was 9.42 ($P < .001$).[41]

Moreover, several studies also suggest that plasma levels of HDL cholesterol were decreased, and levels of TG, VLDL and intermediate-density lipoproteins (IDL) were increased in subjects with sdLDL subclass pattern.[36,42-44]

Dyslipidemia is a common finding in patients with diabetes.[6,45,46]

Several studies have reported the prevalence of dyslipidemia to range from 70%-90% in diabetic patients.[18,47-50]

It was also noted (in 4S and CARE) that the risk of major coronary events in untreated dyslipidemic diabetic patients was 1.5-1.7-fold greater than in untreated nondiabetic patients.[51,52]

The most common pattern of dyslipidemia observed in diabetic patients is elevated TG levels and decreased HDL cholesterol levels. The concentration of LDL cholesterol in diabetic patients is usually similar to that of nondiabetic population; however, Type 2 diabetic patients typically have a preponderance of sdLDL particles, which increases atherogenicity even if concentration of LDL is not significantly increased. Poor glycemic control and the presence of nephropathy is associated with lipid abnormalities in patients with Type 1 diabetes while dyslipidemia is observed in practically all patients of Type 2 diabetes.[45,53-55]

Mohan et al assessed the association of sdLDL with diabetes and CAD in Asian Indians. They reported that sdLDL was significantly higher in diabetic subjects with CAD (16.7 +/- 11.1 mg/dL, $p < 0.05$) and without CAD (11.1

+/- 8.0 mg/dL, $p < 0.05$) as compared to non-diabetic subjects without CAD (7.2 +/- 6.8 mg/dL). Small dense LDL showed a positive correlation with fasting plasma glucose, HbA1c, TC, TG, LDL, TC/HDL ratio and TG/HDL ratio and a negative correlation with HDL cholesterol. The authors suggested that in Asian Indians, sdLDL is associated with both diabetes and CAD and that a TG/HDL ratio could serve as a surrogate marker of sdLDL.[56]

Many prospective and case-control studies have shown a positive association between the serum TG and CAD risk and demonstrated the importance of fasting TG level as an independent risk factor. [57,58]

Austin et al performed a meta-analyses on population-based prospective studies, ensuring that elevations in fasting TG preceded the onset of fatal and nonfatal CHD events. A 88 mg/dL increase in TG was associated with a 32% increase in CHD in men and a 76% increase in CHD in women. After adjusting for HDL-C and other pertinent variables in studies with the data available, there was still a significant increase of CHD by 14% for men and 37% for women.[59,60]

The Asia Pacific Cohort Studies Collaboration performed an individual participant data meta-analysis of prospective studies conducted in the Asia-Pacific region. In the Asian cohorts, stroke and CHD accounted for 41% and 25% of cardiovascular deaths, respectively. After adjustment for age, sex, blood pressure, smoking, and total-to-HDL cholesterol ratio, participants grouped in the highest fifth of TG levels had a 70% greater risk of CHD death, an 80% higher risk of fatal or nonfatal CHD, and a 50% increased risk of fatal or nonfatal stroke compared with those belonging to the lowest fifth. The study concluded that serum TG levels are associated with a risk of developing CVD independently of other major measured risk factors, including HDL cholesterol in the Asia-Pacific region.[61]

Sawant et al reported that prevalence of hypertriglyceridemia was found to be more in men (42.6%) compared to women (17.2%). [2,62,63]

Similar findings were reported by Latheef et al and Gupta et al.

Goel PK reported that high TG and low HDL cholesterol levels are most universal phenomenon observed in Indian patients with CAD than those with normal coronary arteries.[55]

The Framingham Heart Study identified that a low HDL cholesterol level predicted the risk for CAD, independently of other risk factors.[64,65]

Gordon et al found that for each 1 mg/dL decrease in HDL cholesterol, the risk

for CAD increased by 2% to 3% in the population.[66]

South Asians not only have lower HDL levels, but also have a higher concentration of small, less-protective HDL particles, placing them at a higher risk of developing CVD.[34,67]

Lipoprotein(a) has also been identified as a major independent genetic risk factor for CHD in Indians. Studies have revealed that plasma Lp(a) levels are significantly elevated in Indian patients with CHD.[68-73]

Lp(a) like LDL possesses cholesterol ester, triacylglycerol, cholesterol, phospholipids, and a closely associated protein apo B-100; which can bind to LDL receptor. Lp(a) acts as a competitive inhibitor for the action of plasminogen and prevents fibrinolysis. It thereby acts as a dual pathogen which is both atherogenic due to its similarity with LDL and thrombogenic due to apo(a)'s structural resemblance to plasminogen.[74]

Isser et al assessed lipoprotein (a) levels in 50 consecutive young North Indian patients with MI, their first-degree relatives, and age- and sex-matched controls. The mean Lp(a) level was 22.28+5.4 mg/dL in patients with MI, 13.88+5.19 mg/dL in their first-degree relatives and 9.28+22.59 mg/dL in controls. In addition, it was significantly higher in young patients with MI and their relatives as compared to controls. The authors suggested that higher Lp(a) levels represent an important risk factor for CAD in the younger population; also, there is familial clustering of high Lp(a) levels in first-degree relatives of young patients with MI.[75]

Rajasekhar et al demonstrated significant difference in Lp(a) levels between normal coronaries versus single and triple vessel disease. Lp(a) levels correlated positively with vessel severity($P<0.005$) and levels >25 mg/dL were associated with CHD ($P<0.05$) in patients with clinical and angiographic evidence of CHD.[76]

Several other studies report that higher mean levels of Lp(a) are observed in patients with CAD than the controls in India.[69,72,77,78]

It has also been seen that individuals with high blood cholesterol levels have a higher prevalence of hypertension and those with high blood pressure have a higher prevalence of hypercholesterolemia.[79-82]

Pramiladevi et al assessed the lipid profile in hypertensive patients and reported that TC, LDL, Lp(a) and TC/HDL >4.5 were significantly elevated in hypertensive patients compared to controls. Elevation of TC and decrease in HDL was found as the severity of hypertension increased. The commonest

individual lipid fraction abnormality was low HDL in 74% followed by elevated total cholesterol in 52%. Next commonest being TC/HDL >4.5 in 50%, followed by elevated Lp(a) in 36%. Commonest lipid abnormality was abnormal TC/HDL >4.5 and elevated TG together in 86% the and over all prevalence of all forms of dyslipidemia was 90%. In addition, abnormalities in lipid profile antedate the occurrence of stage I hypertension, suggesting the need for lipid profile screening of asymptomatic prehypertensive patients.[83]

Similar findings were reported by several other studies.[84-86]

This finding is significant as both conditions are independent risk factors for the development of CAD and hence can accelerate development of atherosclerosis and lead to adverse cardiovascular outcomes.[80,87]

Recommendations

- Dyslipidemia is a major risk factor for CAD development and Asians tend to have smaller and denser LDL cholesterol, elevated TGs and Lp (a), all of which predisposes them to the early development of CAD (IIa/B).
- Individuals with hypercholesterolemia have a higher prevalence of hypertension and those with high blood pressure have a higher prevalence of hypercholesterolemia. These two conditions can accelerate development of atherosclerosis and lead to adverse cardiovascular outcomes (IIa/C).

Thyroid Dysfunction and Dyslipidemia

Thyroid diseases are one of the commonly occurring endocrine disorders worldwide. About 42 million people in India suffer from varied thyroid disorders.[88]

Thyroid hormones significantly affect lipoprotein metabolism as well as some CVD risk factors, thus influencing the overall CVD risk.[89,90]

A linear positive association has been seen between thyroid-stimulating hormone (TSH) values in the reference range and concentrations of total serum cholesterol, LDL cholesterol, non-HDL cholesterol and TG, and a linear negative association with HDL cholesterol.[91]

Thyroid hormones induce 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, which is the first step in cholesterol biosynthesis. Triiodothyronine (T3) causes an upregulation of LDL receptors, controls the sterol regulatory element-binding protein-2 (SREBP-2), which in turn regulates LDL receptor's gene expression and protects LDL from oxidation.[92]

Thyroid hormones influence HDL metabolism by increasing cholesteryl ester transfer protein (CETP) activity, which exchanges cholesteryl esters from HDL2 to the very low density lipoproteins (VLDL) and TGs to the opposite direction. It stimulates lipoprotein lipase (LPL), which catabolizes the TG-rich lipoproteins, and the hepatic lipase (HL), which hydrolyzes HDL2 to HDL3 and contributes to the conversion of intermediate- density lipoproteins (IDL) to LDL and in turn LDL to sdLDL. Another effect of T3 is the up-regulation of apolipoprotein AV (ApoAV), which plays a major role in TG regulation.[91]

Beyond their effect on lipid profile, thyroid hormones also affect a number of other metabolic parameters related to CVD risk; such as the metabolism and production of adipokines, insulin sensitivity, oxidative stress and BMI or waist circumference.[93-95]

Recommendations

- Thyroid disorders are common among Indian patients (IIa/B).
- Thyroid hormones significantly affect lipoprotein metabolism causing varied effects on cholesterol levels (IIa/B).
- Thyroid dysfunction also predisposes an individual to other cardiovascular risk factors such as the metabolism and production of adipokines, oxidative stress and metabolic syndrome (IIa/B).

Overt Hypothyroidism and its Effect on Lipids

Hypothyroidism has been found to be a very important risk factor for secondary hypercholesterolemia. The prevalence of overt hypothyroidism varies according to different surveys, depending on geographical and the environmental factors such as dietary iodide, goitrogen intake, the genetic characteristic and the age distribution of the population.[88,96]

Hypothyroidism tends to occur more commonly in women than men. Krishna et al found the prevalence in an unselected community population to be 1.4%, with an estimated annual incidence rate of one to two per 1000 women.[97,98]

Menon et al in a population-based study found the prevalence to be 3.9%.[99]

Whereas, Abraham et al found the prevalence of hypothyroidism to be 11.5%.[98]

In the United States National Health and Nutrition Examination Survey (NHANES III), the prevalence of overt hypothyroidism was found to be 0.3%.[100]

Functional studies of the goitrous subjects showed overall prevalence of 5.4% hypothyroidism, 1.9% hyperthyroidism and 7.5% prevalence of autoimmune thyroiditis (by fine needle aspiration biopsy among female goitrous students).[101]

Hypothyroidism causes hypercholesterolemia mainly due to elevation of LDL cholesterol levels, whereas HDL cholesterol concentration is usually normal or even elevated.[102]

In many cases hypothyroidism and hypercholesterolemia co-exist.

Tagami et al studied the prevalence of hypothyroidism in patients with hypercholesterolemia and found it to be 4.3%.[103]

It has been seen that over 90% of overtly hypothyroid patients have hyperlipidemia. Serum TC and LDL cholesterol levels are increased by approximately 30% in patients with overt hypothyroidism.[104]

In hypothyroidism, LDL cholesterol clearance is reduced, probably reflecting reduced expression of LDL receptors on the surface of liver cells. The low activity of CETP and particularly of hepatic lipase in hypothyroidism leads to reduced transport of cholesteryl esters from HDL2 to VLDL, IDL and HDL3. Decreased LPL activity results in reduced conversion of VLDL into LDL

and predisposes to increase in TG, IDL and VLDL with small, dense, highly atherogenic particles.[105]

Several studies have shown a statistically significant increase in fasting TC, TG, and LDL-C concentrations with declining thyroid function.[106-109]

LDL, especially sdLDL is prone for oxidation and can be highly atherogenic. Overt hypothyroidism can lead to increased LDL-C levels that may enhance the formation of oxidized LDL (oxi-LDL), generating foam cells by their uptake by the macrophages, thereby promoting atherogenesis.[110-111]

Overt hypothyroid patients may also present with elevated TG levels, associated with increased levels of VLDL and occasionally fasting chylomicronemia.[92,112]

It has been seen that the VLDL and IDL particles in hypothyroidism are rich in cholesterol and apolipoprotein E, thus resembling β-VLDL particles of type III hyperlipoproteinemia. Therefore, patients homozygous for the apolipoprotein E2 allele can develop full-blown clinical syndrome of the type III hyperlipoproteinemia and become hypothyroid.[92]

Overt hypothyroidism also affects the HDL-C levels. There is an increase in the HDL2 subparticle concentrations in patients with hypothyroidism.[107]

Dullaart et al reported that the changes in HDL, TC, free cholesterol, triacylglycerol and the free cholesterol/cholesteryl ester molar ratio in HDL were inversely-related to the changes in cholesteryl ester transfer activity. Cholesteryl ester transfer activity has been found to be 15% lower during hypothyroidism resulting in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL-C levels.[113]

Lp(a), which has been demonstrated to have a thrombogenic and atherogenic influence has been found to be increased in patients with hypothyroidism, increasing the risk of CVD.[114,115]

Recommendations

- Hypothyroidism is a very important risk factor for secondary hypercholesterolemia and in many cases hypothyroidism and hypercholesterolemia co-exist (IIa/B).
- More than 90% of overtly hypothyroid patients have hyperlipidemia (IIa/B).
- Hypothyroidism is associated with a rise in serum TC, LDL cholesterol, TG and Lp(a) levels. Overt hypothyroidism also enhances the formation of oxidized LDL (oxi-LDL), which is an important for atherogenesis (IIa/B).

Subclinical Hypothyroidism and its Effect on Lipids

Subclinical hypothyroidism (SCH) is defined as a high serum TSH concentration with serum free T4 (fT4) and T3 concentrations within reference ranges.[116-119]

The prevalence of SCH ranges between 4% to10% in the general population and between 7% to 26% in the elderly. Approximately 2%-5% of patients with SCH will progress to overt hypothyroidism annually. The rate of progression is proportional to the baseline serum TSH concentration and is higher in patients with elevated thyroid autoantibodies.[116,120-122]

Estimates of the prevalence of SCH among patients with dyslipidemia ranges from 1.4% to 11.2%.[104,118,119,123]

Although SCH has adverse effect on lipid profile, available reports are controversial.[118,119]

Mya et al investigated the prevalence of SCH and its association with dyslipidemia. They found that 6% of patients had SCH, of which 83% developed dyslipidemia. The authors concluded that SCH was associated with a high prevalence of dyslipidemia.[124]

In a study by Shekhar et al, the SCH group had higher levels of serum TC and LDL cholesterol which was found to be in positive correlation with TSH level. The prevalence of SCH in the study was 8.29% and all of these subjects had dyslipidemia.[118]

Marwaha et al found the prevalence of SCH to be 14.7% in a cross sectional study in India. The only lipid abnormality seen in their study was low HDL and high serum TC, and LDL cholesterol in patients with TSH >10mIU/L. Serum TSH was positively and fT3 and fT4 were negatively correlated with TC and LDL. Atherogenic lipid abnormalities were observed only if TSH was >10mIU/L.[125]

Similar findings were reported by other studies.[126-129]

Pearce et al found that TC, LDL-C, and TG were increased, whereas HDL-C and Lp(a) remain unchanged in subclinically hypothyroid patients.[104]

In another study Caparević et al found that serum cholesterol, LDL-C and apo B were high in patients with SCH.[130]

Efstathiadou et al concluded that patients with SCH did exhibit increased levels of the atherogenic parameters [mainly LDL-C and Lp(a)].[131]

Recommendations

- The prevalence of SCH is probably high in the community and about 2-5% of these patients progress to overt hypothyroidism annually (IIa/A).
- Most studies have shown that in patients with SCH atherogenic lipid abnormalities are observed (↑TC, ↑LDL-C, ↑TG) only if TSH is >10.0 mIU/L (IIa/B).

Cardiovascular Risk in Patients with Overt and Subclinical Hypothyroidism

There is substantial evidence that hypothyroidism alters several of the traditional risk factors for CVD. These studies support a biologically plausible role for hypothyroidism increasing the risk of atherosclerotic CVDs, via increase in circulating levels of highly atherogenic sdLDL particles, mainly due to decreased catabolism and turnover, induction of diastolic hypertension, altered coagulability, and direct effects on vascular smooth muscle.[125,132-135]

The increased LDL-C levels in hypothyroidism may enhance the formation of oxi-LDL, which is highly atherogenic.[110]

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.[136]

Mya et al investigated the prevalence of SCH CAD. They found that CAD was present in 56% of these patients. The authors concluded that SCH was associated with a high prevalence of dyslipidemia and CAD.[124]

Another factor contributing to arteriosclerotic vascular disease in patients with hypothyroidism is the high prevalence of hyperhomocysteinemia.[133]

Elevated homocysteine level is an important risk factor for development of CVD. It causes endothelial dysfunction, vascular impairment and an early decline in renal function. Decline in renal function alone causes elevation of plasma homocysteine levels.[137]

Christ-Crain et al showed that C-reactive protein (CRP) and total homocysteine values increased with progressive thyroid failure and this may count as an additional risk factor for the development of CHD in hypothyroid patients.[138]

Hypothyroidism has been recognized as a cause of secondary hypertension. Saito et al found a strong association between elevated diastolic blood pressure and hypothyroidism.[139]

Fletcher et al also showed a similar finding. The potential mechanism of hypertension in hypothyroidism is not completely understood: changes in circulating catecholamines, their receptors and the renin-angiotensin-aldosterone system and increase in peripheral vascular resistance and arterial stiffness have all been implicated.[132,140-142]

Metabolic syndrome (MetS) is higher in patients with hypothyroidism. MetS is identified as a major risk for development of atherosclerosis, and the prevalence of CVD is 2–3 times higher in individuals with MetS. In a study, Shantha et al and Ganidagli et al showed that hypothyroidism was associated with MetS and females are at more risk.[143,144]

In another study, Erdogan et al found that waist circumference and insulin resistance was higher in the hypothyroid group and prevalence of MetS was 44%.[145]

Hypothyroidism has been shown to induce insulin resistance with impaired translocation of GLUT4 glucose transporters on the plasma membrane.[146,147]

Takumara et al investigated the relationship between thyroid function and carotid intima-media thickness (CIMT). They demonstrated that CIMT is independently associated with thyroid function within the normal reference range, which suggests an increased cardiovascular risk in subjects with low normal thyroid function.[148,149]

In another study Nagasaki et al found that basal CIMT was significantly higher in hypothyroid patients [0·635 ± 0·018 (mean ± SE) mm] than in control subjects (0·559 ± 0·021 mm, $P < 0·005$). They suggested that increased levels of LDL cholesterol and the total/HDL cholesterol ratio have an important role in the increased CIMT in hypothyroid patients.[150]

Hypothyroidism is also associated with an increased incidence of diastolic heart failure. It may be due to decreased heart rate, elevated peripheral vascular resistance, increased diastolic blood pressure and cardiac afterload, reduced blood volume and cardiac preload, and diminished cardiac output. Impaired left ventricular systolic contractility at least during exercise and delayed left ventricular diastolic relaxation at rest and during exercise are common in overt hypothyroidism.[136,148]

Rheumatoid arthritis (RA) patients have an increased risk of developing CVD. RA is an autoimmune disorder and so is hypothyroidism in some cases. Raterman et al determined the prevalence of hypothyroid disorders in RA patients and also the risk of CVD in RA patients with hypothyroid abnormalities. Clinical hypothyroidism was observed three times more often in female RA patients than females in the general population. In female RA patients, clinical hypothyroidism was associated with a four-fold higher risk of CVD in comparison with euthyroid female RA patients independent of the traditional risk factors.[151]

It has been shown that cardiovascular system is very sensitive even to minimal variations of circulating thyroid hormone. Therefore, even SCH may be considered as a true risk factor for the development of CHD. At a younger age, SCH has more severe pathophysiological effects resulting in accelerated vascular disease through dyslipidemia, endothelial dysfunction or a direct effect on myocardium.[118]

In the Rotterdam study, Hak et al found that SCH was highly prevalent in elderly women and was strongly and independently associated with aortic atherosclerosis and MI.[152]

Pucci et al found that hypothyroid patients appear to have an increased incidence of residual myocardial ischemia following acute MI.[135]

SCH may increase cardiovascular risk by altering peripheral vascular resistance and serum lipid and coagulation profiles.[122]

An early event in SCH-related cardiomyopathy, evaluated by Doppler echocardiography and MRI scans showed impairment of diastolic function.[153-155]

Sahin et al investigated the effect of SCH on autonomic activity and demonstrated that SCH modifies cardiac autonomic activity in patients with serum TSH values ≥10 mIU/L, but not in those with TSH levels <10 mIU/L.[156]

Caraccio et al found impaired neuromuscular symptom and muscle energy metabolism in SCH. In their study, maximal power output and VO(2) max were reduced and with increasing workload, patients achieved higher heart rates than controls.[157]

Luboshitzky et al found that about 20% of SCH patients had high blood pressure, mainly diastolic hypertension.[158]

Some of the studies have also found endothelial dysfunction along with higher carotid artery intima-media thickness and increased arterial stiffness in patients with SCH.[159-163]

Gullu et al demonstrated that activities of factor VIII and von Willebrand factor were significantly lower in patients with SCH than in controls, whereas Guldiken et al found that the global fibrinolytic capacity was significantly lower in patients with SCH than in controls, suggesting a relative hypercoagulable state in SCH.[164,165]

Elevated C-reactive protein, L-arginine, asymmetric dimethylarginine concentrations, and insulin resistance, all risk factors for cardiovascular disease, may occur in patients with SCH.[166,167]

Elevated plasma homocysteine concentrations and MetS reported in patients with overt hypothyroidism have not been seen in patients with SCH.[122,168]

Imaizumi et al found that in men but not in women, SCH was associated with ischemic heart disease and mortality independent of age, systolic blood pressure, body mass index, cholesterol, smoking, erythrocyte sedimentation rate, or presence of diabetes mellitus. There was no association with cerebrovascular disease.[169]

In a recent study, McQuade et al assessed the effects of hypothyroidism (TSH >10μU/L), moderate SCH (TSH: 6.1-10 μU/L), and mild SCH (TSH 3.1-6.0 μU/L) on cardiovascular risk factors, CHD prevalence, and all-cause mortality in patients at high risk for CHD. All-cause mortality was higher in both genders in hypothyroid and moderate SCH patients, but not in mild SCH patients.[170]

Park et al explored the association between SCH and CAD in apparently healthy subjects. They found that SCH subjects who were at an intermediate-to-high risk of developing CAD were significantly more likely to exhibit occult CAD than euthyroid subjects, especially in men with SCH. They suggested that mild thyroid failure independently contributes to the development of CAD.[171]

Rodondi et al did a metaanalysis involving more than 50,000 patients to evaluate the controversial association between SCH and CVD outcomes. They found that the risk of CHD events and CHD mortality increased with higher TSH concentrations and concluded that SCH is associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels, particularly in those with a TSH concentration of ≥10 mIU/L.[172]

Similar results on CVD mortality in SCH patients were reported by Singh et al.[173]

These studies do not provide a clear view as to whether SCH exerts deleterious effects on the cardiovascular system with the consequences of increased morbidity and mortality. In future, well designed prospective randomized studies with age stratified groups and vascular events as the primary endpoint are required and it is anticipated that these studies will give the proper answer whether SCH is associated with increased cardiovascular outcomes and if early substitution therapy with levothyroxine will be able to reverse the ischemic heart disease risk in affected patients with SCH.

Recommendations

- Overt hypothyroidism is associated with a definite risk of atherosclerotic CVD, mainly due to increase in circulating levels of highly atherogenic sdLDL particles, induction of diastolic hypertension, endothelial dysfunction and altered coagulability (IIa/B).
- SCH with TSH >10mIU/L is a definite risk factor for CVD and all such cases should be considered as high risk (IIa/B).

Hyperthyroidism and Lipid Changes

Overt hyperthyroidism is defined as a serum TSH level <0.1 mIU/L with serum fT4, T3, or fT3 concentrations above the normal reference range. Subclinical hyperthyroidism is defined as low serum TSH concentration (<0.4 mIU/L) in an asymptomatic patient with normal serum T3 and T4 concentration.[174]

Hyperthyroidism is much less common than hypothyroidism and the prevalence varies from region to region. Rizos et al found that the incidence in general population was 2.2%.[92,116,175]

Other epidemiological studies have reported that the overall prevalence of overt hyperthyroidism ranges from 0.5-1.2%.[88,98,100,108]

Whereas, prevalence of subclinical hyperthyroidism in the general population is between 0.7 and 12.4%. Approximately 1-5% of patients with subclinical hyperthyroidism develop overt disease annually.[116,176-178]

In India, the prevalence has been found to vary from 0.5-3.9% for subclinical and 1.2-1.3% for overt hyperthyroidism. More than a third of community-detected hyperthyroid cases have positive anti-TPO antibodies, and about 39% of these subjects have goiter.[88,174]

In Nepal, Regmi et al found the prevalence of overt hyperthyroidism and subclinical hyperthyroidism to be 3.3% and 4.6% respectively.[179]

The incidence of hyperthyroidism has been found to be very low in patients with dyslipidemia. Tsimihodimos et al found that hyperthyroidism was present in only 1.2% of patients attending their lipid clinic.[180]

Despite the increased activity of the HMG-CoA reductase, levels of TC, LDL cholesterol, apolipoprotein B and Lp(a) tend to decrease in patients with clinical or subclinical hyperthyroidism, due to increased bile excretion of cholesterol and increased LDL receptor gene expression resulting in enhanced LDL receptor-mediated catabolism of LDL particles. Furthermore, HDL cholesterol levels are also decreased in hyperthyroidism due to increased CETP-mediated transfer of cholesteryl esters from HDL to VLDL and increased HL-mediated catabolism of HDL-2. Triglyceride levels remain unchanged. Hyperthyroidism can also result in enhanced LDL oxidability.[102]

Duntas et al found an enhanced excretion of cholesterol and an increased turnover of LDL cholesterol resulting in a decrease of total and LDL cholesterol, whereas HDL cholesterol was decreased or not affected.[89]

In another study by Kung et al, hyperthyroid patients had lower concentrations of apo A, TC, LDL-C, HDL-C, and apo B, but higher apo A-I concentrations compared with age-matched controls.[181]

Similar results were found by Muls et al.[182]

Other qualitative lipid changes seen in hyperthyroidism include increased levels of oxidized LDL, higher contents of thiobarbituric acid-reactive substances and dienes in LDL, low paraoxonase activity in HDL particles, and lower LDL content in antioxidant vitamin E and β-carotene.[92]

Recommendations

- Clinical and subclinical hyperthyroidism is associated with decreased levels of TC, LDL cholesterol, HDL cholesterol and Lp(a) (IIa/B).
- Triglyceride levels remain unchanged and there is enhanced LDL oxidation (IIa/B).

Hyperthyroisim and Cardiovascular Risk

Hyperthyroidism is associated with tachycardia, systolic hypertension, atrial fibrillation and heart failure, as well as increased cardiovascular and cerebrovascular mortality. Its hemodynamic repercussions are due to the multiple effects, both direct and indirect, of thyroid hormones on the cardiovascular system. Hyperthyroidism can trigger angina and MI in patients with CHD, perhaps by stimulating metabolism and increasing the production of free radicals from the oxidation of LDL cholesterol, leading to endothelial dysfunction.[105]

In hyperthyroidism, hemodynamic changes result mainly from increased β1-adrenergic activity. Increased triiodothyronine levels exert positive inotropic and chronotropic effects, leading to enhanced heart rate and systolic contractility and, consequently, increased cardiac output. It also stimulates sarcoplasmic reticulum Ca-ATPase, leading to systolic and diastolic dysfunction. Moreover, triiodothyronine reduces peripheral vascular resistance, causing a decrease in diastolic blood pressure and cardiac afterload, which further raises cardiac output. Decreased vascular resistance accounts for activation of renin-angiotensin-aldosterone system, which increases blood volume and cardiac preload, augmenting cardiac output even more.[148]

Biondi et al found that even patients with subclinical hyperthyroidism had significantly higher average heart rate, enhanced systolic function, impaired diastolic function with prolonged isovolumic relaxation time, and increased left ventricular mass compared with euthyroid subjects.[183]

Westerink et al investigated the effects of TSH levels and increased risk of new vascular events and mortality in patients with clinical manifest vascular diseases. They found that an increase in 1 unit of TSH was associated with a 33% higher risk (hazard ratio [HR]) for the occurrence of MI, adjusted for age, gender, renal function, and smoking. In patients with a body mass index (BMI) below the median of 26.7 kg/m^2 the HR per unit TSH for MI was 1.55 compared to 1.18 in patients with a BMI ≥26.7 kg/m^2. Visceral adipose tissue thickness below the median (≤8.8 cm) was associated with higher HR per unit TSH for MI compared to visceral adipose tissue thickness >8.9 cm. They concluded that higher TSH levels within the normal range was associated with an increased risk of MI, in patients with clinical manifest vascular disease.[184]

Patients with overt hyperthyroidism have a hypercoagulable state and an increased risk of thrombosis.[185]

Erem et al investigated the markers of endogenous coagulation and fibrinolysis in patients with subclinical hyperthyroidism. They found that factor X activity was significantly increased in patients with subclinical hyperthyroidism. Total cholesterol and LDL-C levels were significantly higher, but no differences could be found in coagulation/fibrinolysis parameters. They concluded that increased factor X activity in patients with subclinical hyperthyroidism represent a potential hypercoagulable state, which might augment the already existing risk for atherosclerotic complications. Also, subclinical hypothyroid patients exhibit a more atherogenic lipid profile compared with healthy individuals. Therefore, SCH is also associated with an increased risk of CVD.[186]

In a study, Sawin et al reported a 3-fold increased risk of atrial fibrillation over 10 years in men and women at least 60 years of age with serum TSH ≤0.1 mIU/L with endogenous and exogenous subclinical hyperthyroidism.[187]

In another study Auer et al found a 5-fold increased risk of atrial fibrillation in individuals with endogenous subclinical hyperthyroidism (age not specified) and TSH lower than 0.4mIU/L compared with euthyroid individuals.[188]

Several other epidemiological studies have examined cardiovascular risk in patients with subclinical hyperthyroidism with varying conclusions. Parle et al measured baseline TSH levels in individuals ≥ 60 years of age and found that all-cause and cardiovascular mortality were greater in subjects with serum TSH levels <0.5 mIU/L at 2, 3, 4, and 5 years of follow-up.[189]

Gussekloo et al found a similar finding in a cohort of individuals over the age 85 years.[190]

Whereas Walsh et al found no increased frequency of CAD or cardiovascular mortality in a younger population.[191]

No studies have demonstrated an increased incidence of arterial embolism in patients with subclinical hyperthyroidism. However, atrial fibrillation due to overt hyperthyroidism is a known risk factor for arterial embolism.

Dorr et al reported that patients with subclinical hyperthyroidism had about 5.2-fold elevated risk for atrial fibrillation while for overt hyperthyroidism there was a 1.7 fold elevated risk for cardiovascular diseases and about 1.7 fold increased risk of cardiovascular mortality.[192]

Recommendations

- Hyperthyroidism is associated with an increased risk of ischemic heart disease and congestive heart failure (IIa/B).
- Overt hyperthyroidism can cause atrial fibrillation and arterial embolism (IIa/B).
- Arterial embolism is not common in patients with subclinical hyperthyroidism (IIb/C).

Management of Overt Hypothyroidism in Dyslipidemia

Treatment of the thyroid disorder potentially improves dyslipidemia and reduces risk for CVD.[193]

Various studies have shown that administration of substitution therapy with levothyroxine (LT4) significantly improves lipid metabolism abnormalities. A period of 4-6 weeks of thyroxine replacement therapy is usually needed to correct dyslipidemia in overt hypothyroidism. In general, changes in serum lipoproteins in hypothyroid patients are correlated with changes in fT4. Wiseman et al investigated prospectively 52 patients with primary hypothyroidism treated with LT4. There was a significant reduction in TC, HDL cholesterol, LDL cholesterol, and apolipoprotein-A1 and -B after thyroid hormone replacement.[194]

Gullu et al assessed the effects of LT4 therapy on the coagulation parameters in patients with overt hypothyroidism. Bleeding time, PT, APTT and clotting time decreased significantly ($P < 0.05$ for all) and factor VIII activity, vWF activity and platelet count increased significantly in overtly hypothyroid patients after LT4 therapy ($P < 0.01$, $P < 0.01$ and $P < 0.05$ respectively).[164]Elder et al found a dramatic reduction of TC levels in overt hypothyroid patients with higher baseline TSH levels.[195]

Arem et al assessed the effect of LT4 therapy on lipoprotein fractions in patients with overt hypothyroidism. There was a significant reduction in TC, and apo B with little effect on Lp(a).[196]

Thyroxine treatment of overt hypothyroid patients might exacerbate myocardial ischaemia in those with underlying CAD due to positive inotropic and chronotropic effects of thyroid hormone. Starting treatment at lower doses in these patients e.g., 25 µg per day is justified. The traditional recommendation has been gradual titration of the thyroxine dose upward to euthyroidism in 12.5 to 25.0 µg increments at intervals of 4–6 weeks with monitoring of TSH levels and ECG.[197]

Verdugo et al observed a decrease in HDL2 cholesterol with no changes in HDL3 cholesterol in patients with overt hypothyroidism. The decrease in HDL2 cholesterol correlated with that for apo AI.[198]

Tzotzas et al examined the influence of overt hypothyroidism before and during

LT4 treatment, on Lp(a), other lipoproteins, and apolipoproteins. They found that in overt hypothyroid patients, levels of TC, LDL-C and apo B decreased significantly after the return to euthyroid state. Body mass index (BMI), Lp (a) and TG levels also decreased significantly during LT4 treatment.[114]

After 1 year of euthyroidism, 97% of hypothyroid patients showed a significant decrease of common carotid artery (CCA) IMT ($P < 0.0001$) to a level comparable to normal controls.[150]

These studies confirm the beneficial effects of LT4 therapy on lipid profile and cardiovascular risk factors in patients with overt hypothyroidism. Hence, all patients with hyperlipidemia and overt hypothyroidism should be treated with LT4. Once serum TSH values have normalized, usually by 2 to 4 months of adequate LT4 therapy, serum lipid values should be repeated. Up to a 30% to 50% decrease in the ratio of TC to HDL cholesterol can be expected with LT4 treatment. If adequate response is not seen with LT4 therapy alone, therapeutic lifestyle changes should be instituted and lipid-lowering medications should be added. It is preferable to start statins, if required, after patients become euthyroid, as overt hypothyroidism may be a risk factor for statin-associated myopathy. If in doubt creatine kinase levels should be checked.[104]

In some cases statins are combined with fibrates for controlling severe dyslipidemia. Caution should be exercised as combination of statins with fibrates further increases risk of myopathy.

Different clinical situations in the management of hypothyroidism with dyslipidemia;

1. In patients without Coronary Artery Disease (CAD): Make the patient euthyroid first with LT4 therapy. Repeat lipid profile and based on lipid levels use statins as per NCEP guidelines.[199]
2. In patients with CAD (including acute coronary syndrome): Use statins as per NCEP guidelines and for hypothyroidism patients, should be simultaneously started on LT4 therapy (25 mcg daily and increased by 25mcg/day every 2 to 4 weeks until the TSH level normalizes).[200]

Recommendations

- All patients with hyperlipidemia and overt hypothyroidism should be treated with LT4 therapy first. A period of 4-6 weeks of replacement therapy is usually needed to correct the dyslipidemia (IIa/B).
- As LT4 treatment may exacerbate myocardial ischaemia in patients with

underlying CAD, start treatment at lower doses (25 µg/day) and titrate gradually (12.5 to 25.0 µg increments) at intervals of 4–6 weeks with monitoring of TSH levels and ECG (IIa/B).

- If adequate response is not seen with LT4 therapy alone after 4 to 6 weeks of therapy administer lipid-lowering medications (IIa/B).
- Use of statin in hypothyroidism with dyslipidemia should be customized
  - No known underlying CAD or risk of CAD-Wait till patient becomes euthyroid and repeat lipid profile and proceed according to NCEP guidelines (IIa/B).
  - In presence of underlying CAD or acute coronary syndrome start statin along with LT4 replacement (IIa/B).
- Use of statin or fibrates alone or in combination in patients with dyslipidemia and uncontrolled hypothyroidism carries a higher risk of myopathy (IIa/A).
- Risk of myopathy may also be associated with the co - administration of statins with LT4 (IIa/B).

Management of Subclinical Hypothyroidism in Dyslipidemia

It is generally agreed that thyroid replacement therapy has beneficial effects on serum lipid profile and CVD risk in overt hypothyroid patients, but no clear consensus has been established regarding the treatment of SCH subjects. This is due to lack of clear information on whether and to what degree does SCH affect lipid profile, what are the overall effects of substitution therapy on morbidity and mortality in these patients and whether all SCH patients would benefit from thyroxine replacement therapy.[92,201,202]

Some of the points put forth by researches in favor of providing treatment to patients with SCH are that treatment will prevent patient's progression to overt hypothyroidism and will also reduce the future risk of cardiovascular disease. However, these findings are yet to be confirmed in large prospective randomised trials.[197]

Some clinical studies have shown a beneficial effect of substitution therapy on lipid parameters in patients with SCH.

Milionis et al evaluated the Lp (a) levels and apo (a) phenotypes in patients with SCH compared to healthy controls. Though they could not find a causal effect of thyroid dysfunction on Lp(a) in patients with SCH, LT4 treatment was beneficial, especially in patients with increased baseline Lp(a) levels and apo(a) isoforms.[202]

Fanklyn et al found that LT4 treatment in patients with SCH resulted in reductions in total and LDL cholesterol with increasing LT4 dose ($P < 0.001$).[203]

Danese et al reported that serum TC concentration changed during LT4 treatment in patients with SCH. The mean decrease in the serum TC concentration was -7.9 mg/dL and the decline was directly proportional to its baseline concentration.[204]

In the 5th Tromso study, Iqbal et al showed a significant and positive correlation between serum TSH levels and serum TC and LDL-C levels. They observed a significant reduction in the Apo B levels after thyroxine medication. Also subjects with serum TSH levels in the range of 0.2-2.0 mIU/L had the serum TC and LDL-C levels reduced significantly.[205]

Monzani et al and Nagasaki et al suggested that increased levels of LDL cholesterol and the total/HDL cholesterol ratio have an important role in the

increased common carotid intima-media thickness in hypothyroid patients and showed that LT4 replacement therapy was able to improve both the atherogenic lipoprotein profile and intima-media thickening.[150,206]

Tanis et al found that thyroid substitution treatment in patients with hypercholesterolaemia and SCH decreased total plasma cholesterol by about 15 mg/dL.[207]

Data for some of the other studies do not support these beneficial effects.

Efstathiadou et al found no significant changes in serum lipid profiles, except for a decrease in HDL cholesterol ($P<0.05$) after restoration of a euthyroid state with incremental doses of LT4 in patients with SCH.[131]

In a metaanalysis, Villar et al evaluated the effects of thyroid hormone replacement for SCH. Twelve trials of 6 to 14 months duration involving 350 people were included. They found that LT4 replacement therapy for SCH did not result in improved survival or decreased cardiovascular morbidity, though some parameters of lipid profiles and left ventricular function may show improvement.[208]

Kong et al randomly assigned 40 patients with SCH to LT4 treatment versus placebo and found no significant differences in lipid measurements between the two groups after 6 months.[209]

These data raise a significant query as to whether all SCH patients would benefit from thyroxine replacement therapy or such therapy should be reserved for selected subgroups. Furthermore, there are no sufficiently large clinical trials to date that have showed a significant lipid-lowering benefit with LT4 therapy alone. Therefore, in patients diagnosed with both SCH and hyperlipidemia, therapeutic lifestyle changes should be instituted immediately and lipid-lowering medications added as appropriate, regardless of whether or not LT4 therapy is instituted.[104]

Thyroid substitution with SCH is best used if serum TSH concentration is >10 mIU/L or if patients have high initial cholesterol levels, are elderly, smokers or if positive for TPO-Ab. If TSH levels are between 4.5 and 10 mIU/L, they should not be routinely treated, but patients with these levels should have thyroid function tests repeated at 6-12 month intervals.[116]

The usual requirement is 50 to 75 μg/day of LT4. Patients can be started with a dose of 25 to 50 μg/day. Serum TSH should be checked after 8 weeks, and the dose should be adjusted accordingly. Once a normal serum TSH level has been achieved, it should be measured again after 6 months and then annually.[210-213]

Recommendations

- There is no clear consensus on whether thyroid replacement therapy with LT4 has beneficial effects on serum lipid profile and CVD risk in SCH patients (IIb/C).
- Thyroid substitution in patients with SCH is recommended if serum TSH is >10 mIU/L, or if patients have high initial cholesterol levels, are elderly, smokers or are positive for TPO-Ab (IIa/B).
- Replacement therapy should be started with a dose of 25 to 50 µg/day of LT4. Once euthyroid, TSH should be re-measured after 6 months and then annually (IIa/B).
- If TSH levels are between 4.5 and 10 mIU/L, routine treatment is not required. Monitoring should be done by repeating thyroid function tests every 6-12 months (IIa/B).
- A repeat lipid profile is recommended after euthyroid state is achieved (IIa/B).

Management of Hyperthyroidism in Dyslipidemia

The treatment of hyperthyroidism is directed towards lowering the serum concentration of thyroid hormones and to reestablish a eumetabolic state with lowest incidence of hypothyroidism. There are currently three available modalities of treatment, all of which are effective. These include antithyroid drugs (ATDs), radioactive iodine (^{131}I) and surgery.

The ATDs, methimazole and propylthiouracil, inhibit thyroid hormone biosynthesis and are useful either as a primary form of therapy or to lower thyroid hormone levels before (and in some cases after) radioactive iodine therapy or surgery. Initial daily doses of methimazole generally range from 10 to 40 mg, and for propylthiouracil, 100 to 600 mg. When used as primary therapy, they are usually given for 6 months to 2 years. Beta blockers (propranolol) and iodides are used as adjunctive therapy to offer prompt symptomatic relief in hyperthyroid patients.[214,215]

The impact of treatment of hyperthyroidism on the lipid levels is not clear. Treatment with antithyroid drugs has been associated with elevated total and LDL cholesterol levels in some studies. Triglycerides are not affected by antithyroid treatment. HDL, apoB, apoA1, Lp(a) levels have been found to be increased or unchanged after treatment.[148,182,216,217]

The management of lipid levels in patients with hyperthyroidism should be based on the NCEP guidelines.[199]

Sewerynek et al suggested that treatment with methimazole in patients with hyperthyroidism can be protective against the oxidative stress induced by overproduction of thyroid hormones.[218]

Kung et al demonstrated that euthyroidism was associated with normalization of serum TC, LDL-C, and apo B within 1 month of treatment with radioactive iodine in hyperthyroid patients. However, apo A required 4 months to normalize, and HDL-C and apo A-I were still abnormal 6 months after radioactive iodine.[181]

A review of guidelines promulgated by various professional groups has shown a uniform uncertainty about the appropriate management of subclinical hyperthyroidism. Some did not opine and others showed no agreement on benefits of detecting/treating subclinical hyperthyroidism. In 2005, an expert

panel composed of members of the American Thyroid Association, The Endocrine Society, and The American Association of Clinical Endocrinologists concluded that treatment should be offered to "elderly" individuals and those with other risk factors (especially cardiac disease and osteoporosis) and whose serum TSH levels are <0.1 mIU/L. The panel also concluded that the evidence was insufficient to recommend therapy for patients with serum TSH between 0.1– 0.45 mIU/L.[116,219]

Recommendations

- The impact of treatment of hyperthyroidism on lipid levels is not clear (IIa/B).
- Management of dyslipidemia in patients with hyperthyroidism should be according to NCEP guidelines and not based on thyroid status (IIa/B).

Screening for Thyroid Dysfunction in Patients with Dyslipidemia

Biochemical screening for thyroid dysfunction is of paramount importance in all dyslipidemic patients, as well as in all patients with unexpected improvement or worsening of their lipid profile to rule out covert hypothyroidism as a frequent cause of secondary hyperlipoproteinemia, and to allow successful treatment of familial hyperlipoproteinemia.[102,220]

In a study, Mahajan et al found that overt hypothyroid patients had hypercholesterolemia, which is an important risk factor for causing CVD. They also found a significant positive correlation between TSH and TC ($r = 0.916$, $p<0.001$). This positive correlation between thyroid hormone and TC suggests the role of hormone in enhancing lipid metabolism. They recommended screening of TC level in hypothyroid patients which would help to take preventive action for occurrence of CVD.[221]

Vice versa all patients with hypercholesterolemia (and hypertriglyceridemia) should be screened for hypothyroidism before being given specific lipid-lowering drug therapy.[222]

Sharma et al concluded that even SCH patients may benefit by early diagnosis and treatment, firstly by preventing the progression to overt hypothyroidism and secondly by decreasing the risk of death from CVD by starting appropriate therapy to improve lipid parameters.[117]

In one metaanalysis, SCH was determined to be two to three times more common in patients with elevated TC levels than in patients with normal fasting serum lipids.[207]

From the data discussed above, all patients with high blood sugar, MetS or cardiovascular disease should be screened for thyroid dysfunction.[223]

Hypothyroidism can cause secondary hypercholesterolemia and myopathy and one of the common side effects of statin therapy is myopathy. Therefore, before starting hypolipidemic therapy, the evaluation of thyroid function is needed. Thyroid failure is associated with increased levels of creatinine kinase (CK), which are further elevated by initiation of statin therapy.[224]

The American Thyroid Association has recommended that all patients with hypercholesterolemia should be screened for thyroid dysfunction. This approach has been demonstrated to be cost-effective. The preferred test for

screening is measurement of TSH using a sensitive immunometric or similar assay, because of its superior sensitivity and specificity. If the serum TSH value is elevated, some measure of the serum fT4 concentration should be obtained to discriminate between overt and subclinical disease.[213,225]

Uniform national guidelines for screening for thyroid disease with serum TSH levels have not been established. The American Thyroid Association recommends screening by measurement of serum TSH beginning at the age of 35 years and every 5 years thereafter. The evidence in favor of screening is particularly compelling in women, but it can also be justified for men as a relatively cost-effective measure in the context of the periodic health examination. Persons with symptoms and signs potentially attributable to thyroid dysfunction and those with risk factors for its development may require more frequent serum TSH testing.

The American College of Physicians acknowledges that though treatment for subclinical thyroid dysfunction is controversial, screening to detect thyroid dysfunction may be indicated in women older than 50 years.[211]

Recommendations

- Universal screening is indicated for thyroid disorders in all patients with dyslipidemia. Otherwise screening should begin at the age of 35 years and continued every 5 years thereafter. In persons with symptoms and signs of thyroid dysfunction and those with risk factors for its development, more frequent serum TSH testing may be required (IIa/B).
- The preferred test for screening is the measurement of TSH. If the TSH is elevated, measurement of serum T4 is required to differentiate between overt and subclinical thyroid disease (IIa/B).

Summary of Recommendations

Introduction

Recommendations

- Dyslipidemia is a major risk factor for development of atherosclerosis and coronary artery disease (I/A).
- Atherogenic dyslipidemia is characterized by elevated serum TG, small dense LDL particles, and reduced serum high-density lipoprotein cholesterol (IIa/B).
- Asians are inherently prone to have atherogenic dyslipidemia, elevated Lp(a) levels, increased incidence of metabolic syndrome (MetS) and diabetes mellitus (DM) and hence early cardiovascular event (IIa/B).

Dyslipidemia and Cardiovascular Risk

Recommendations

- Dyslipidemia is a major risk factor for CAD development and Asians tend to have smaller and denser LDL cholesterol, elevated TGs and Lp (a), all of which predisposes to the early development of CAD (IIa/B).
- Individuals with hypercholesterolemia have a higher prevalence of hypertension and those with high blood pressure have a higher prevalence of hypercholesterolemia. These two conditions can accelerate development of atherosclerosis and lead to adverse cardiovascular outcomes (IIa/C).

Thyroid Dysfunction and Dyslipidemia

Recommendations

- Thyroid disorders are common among Indian patients (IIa/B).
- Thyroid hormones significantly affect lipoprotein metabolism causing varied effects on cholesterol levels (IIa/B).
- Thyroid dysfunction also predisposes an individual to other cardiovascular risk factors such as the metabolism and production of adipokines, oxidative stress and metabolic syndrome (IIa/B).

Overt Hypothyroidism and Effect on Lipids

Recommendations

- Hypothyroidism is a very important risk factor for secondary hypercholesterolemia and in many cases hypothyroidism and hypercholesterolemia co-exist (IIa/B).
- More than 90% of overtly hypothyroid patients have hyperlipidemia (IIa/B).
- Hypothyroidism is associated with a rise in serum TC, LDL cholesterol, TG and Lp(a) levels. Overt hypothyroidism also enhances the formation of oxidized LDL (oxi-LDL), which is important an important cause for atherogenesis (IIa/B).

Subclinical Hypothyroidism and Effect on Lipids

Recommendations

- The prevalence of SCH is probably high in the community and about 2-5% of these patients progress to overt hypothyroidism annually (IIa/A).
- Most studies have shown that in patients with SCH atherogenic lipid abnormalities are observed (↑TC, ↑LDL-C, ↑TG) only if TSH is >10.0 mIU/L (IIa/B).

Cardiovascular Risk in Patients with Overt and Subclinical Hypothyroidism

Recommendations

- Overt hypothyroidism is associated with a definite risk of atherosclerotic CVD mainly due to increase in circulating levels of highly atherogenic sdLDL particles, induction of diastolic hypertension, endothelial dysfunction and altered coagulability (IIa/B).
- SCH with TSH >10mIU/L is a definite risk factor for CVD and all such cases should be considered at high risk (IIa/B).

Hyperthyroidism and Lipid Changes

Recommendations

- Clinical and subclinical hyperthyroidism is associated with decreased levels of TC, LDL cholesterol, HDL cholesterol and Lp(a) (IIa/B).
- Triglyceride levels remain unchanged and there is enhanced LDL oxidation (IIa/B).

Hyperthyroidism and Cardiovascular Risk

Recommendations

- Hyperthyroidism is associated with an increased risk of ischemic heart disease and congestive heart failure (IIa/B).
- Overt hyperthyroidism can cause atrial fibrillation and arterial embolism (IIa/B).
- Arterial embolism is not common in patients with subclinical hyperthyroidism (IIb/C).

Management of Overt Hypothyroidism in Dyslipidemia

Recommendations

- All patients with hyperlipidemia and overt hypothyroidism should be treated with LT4 therapy first. A period of 4-6 weeks of replacement therapy is usually needed to correct the dyslipidemia (IIa/B).
- As LT4 treatment may exacerbate myocardial ischaemia in patients with underlying CAD, start treatment at lower doses (25 µg/day) and titrate gradually (12.5 to 25.0 µg increments) at intervals of 4–6 weeks with monitoring of TSH levels and ECG (IIa/B).
- If adequate response is not seen with LT4 therapy alone after 4 to 6 weeks of therapy administer lipid-lowering medications (IIa/B).
- Use of statin in hypothyroidism with dyslipidemia should be customized
    - No known underlying CAD or risk of CAD-Wait till patient becomes euthyroid and repeat lipid profile and proceed according to NCEP guidelines (IIa/B).
    - In presence of underlying CAD or acute coronary syndrome start statin along with LT4 replacement (IIa/B).
- Use of statin or fibrates alone or in combination in patients with dyslipidemia and uncontrolled hypothyroidism carries a higher risk of myopathy (IIa/A).
- Risk of myopathy may also be associated with the co - administration of statins with LT4 (IIa/B).

Management of Subclinical Hypothyroidism in Dyslipidemia

Recommendations

- There is no clear consensus on whether thyroid replacement therapy with LT4 has beneficial effects on serum lipid profile and CVD risk in SCH patients (IIb/C).
- Thyroid substitution in patients with SCH is recommended if the serum TSH is >10 mIU/L, or if patients have high initial cholesterol levels, are elderly, smokers or are positive for TPO-Ab (IIa/B).
- Replacement therapy should be started with a dose of 25 to 50 µg/day of LT4. Once euthyroid, TSH should be re-measured after 6 months and then annually (IIa/B).
- If TSH levels are between 4.5 and 10 mIU/L, routine treatment is not required. Monitoring should be done by repeating thyroid function tests every 6-12 months (IIa/B).
- A repeat lipid profile is recommended after euthyroid state is achieved (IIa/B).

Management of Hyperthyroidism in Dyslipidemia

Recommendations

- The impact of treatment of hyperthyroidism on lipid levels is not clear (IIa/B).
- Management of dyslipidemia in patients with hyperthyroidism should be according to NCEP guidelines and not based on thyroid status (IIa/B).

Screening for Thyroid Dysfunction in Patients with Dyslipidemia

Recommendations

- Universal screening is indicated for thyroid disorders in all patients with dyslipidemia. Otherwise screening should begin at the age of 35 years and continued every 5 years thereafter. In persons with symptoms and signs of thyroid dysfunction and those with risk factors for its development, more frequent serum TSH testing may be required (IIa/B).
- The preferred test for screening is measurement of TSH. If the TSH level is elevated, measurement of serum T4 is required to differentiate between overt and subclinical thyroid disease (IIa/B).

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