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SUB CLINICAL HYPOTHYROIDISM AND CARDIOVASCULAR RISK

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ABSTRACT

Thyroid diseases are common endocrine abnormalities around the world. Thyroid hormones play an important role in regulating different metabolic functions. According to the clinical presentation, hypothyroidism is classified as subclinical, mild and overt. Subclinical hypothyroidism (SCH) has been correlated with cardiovascular system due to its major impact on lipids and blood pressure (BP). There are many studies supporting the fact that patients with hypothyroidism are prone to develop a greater cardiovascular risk especially in the patients with thyroid-stimulating hormone (TSH) >10mU/l and thyroxine therapy should be recommended for these patients. But the association between the sub clinical hypothyroidism and cardiovascular disease is still controversial. Our study will investigate the relation between SCH, CVD and associated mortality. So, the main aim of this narrative review is to assess the thyroid dysfunction i.e. sub clincal hypothyroidism and its impact on cardio vascular system, in order to establish specific preventive recommendations and minimize mortality due to CVD. To accomplish these objectives, an updated search of Google scholar and PubMed was conducted for the most recent articles investigating the SCH and its risk on CVD.

KEYWORDS: Thyroid hormones, Subclinical hypothyroidism, metabolism, Cardiovascular diseases.

INTRODUCTION

Thyroid diseases are characterized as frequent endocrine disorder that affects the structure and function of the thyroid gland. Hypothyroidism is defined as insufficient thyroid hormone

production by the thyroid gland, which can be severe or moderate.[1] Subclinical hypothyroidism (SCH), a relatively common disorder which is defined as an isolated elevation of thyroid-stimulating hormone (TSH) levels with a normal free thyroxine (fT4) and fT3 level. The most important and sensitive test for screening of thyroid disorders is Serum TSH measurement because it has a Log Linier relationship with circulating thyroid hormone levels. A two times change in Free Thyroxin (FT4) level changes the TSH level 100 times. So, serum TSH measurement is necessary for diagnosis of mild thyroid failure when the peripheral thyroid hormone levels are within normal laboratory range.[2]

According to various studies it has been reported that prevalence of subclinical hypothyroidism in the developed world is about 4-15%.[3,4] and is affected by different factors like age, sex, race, region, diet and method of TSH measurement.[2] The condition is associated with cardio vascular risk factors like high cholesterol, hypertension due to effect of thyroid hormones on lipid metabolism. Generally, it is observed that approximately 90% of overt hypothyroid individuals have hyperlipidema whereas the triglyceride (TG) , low density lipoprotein (LDL-C) and high density lipoprotein (HDL-C) may be normal or slightly increased resulting in an unfavorable ratio of the LDL-C to HDL-C which is commonly found in cardiovascular diseases[5] but the effect of subclinical hypothyroidism (SCH) on hyperlipidemia is not so much clear[6,7,8] Though the clinical significance of mild thyroid dysfunction (subclinical thyroid disease) is unknown, studies suggest that an elevated TSH level when left untreated may come up with cardiovascular diseases that may lead to the life threatening condition.

The treatment of SCH is generally considered only for patients who are pregnant, infertile, exhibit associated symptoms, or have a high risk of development to overt hypothyroidism.(8) Although, the benefits and risks of treating the sub clinical hypothyroidism still remain controversial however American Thyroid Association recommends that adults should be screened for thyroid dysfunction by measurement of the serum thyrotropin concentration, beginning at age 35 years and every 5 years thereafter.[9]

Both subclinical and overt thyroid dysfunction are considered to be correlated with an increased cardiovascular (CV) risk.[10,11] This review will cover role of thyroid hormone in normal functioning of human body. This narrative review will mainly focus on etiology, symptoms and epidemiology of sub clinical hypothyroidism and will offer insight into studies

on role of thyroid hormones in metabolism of lipids and its influence toward risk factors of cardio vascular diseases (CVD) with associated mortality.

So, the main aim of this review is to assess the thyroid dysfunction i.e. sub clincal hypothyroidism and its impact on cardio vascular system, in order to establish specific preventive recommendations and minimize mortality due to CVD. To accomplish these objectives, an updated search of Google scholar and PubMed was conducted for the most recent articles investigating the SCH and its risk on CVD.

SYNTHESIS OF THYROID HORMONE

The thyroid hormone is primarily responsible for controlling metabolism, growth, and many other body functions. Thyroid is a butterfly shaped organ, known as the largest endocrine gland in vertebrates and is situated in the neck below the thyroid cartilage which forms Adam's apple. The isthmus, medial region between two lobes of thyroid is located in inferior to the cricoid cartilage. The tissue of thyroid hormone is composed primarily with thyroid follicles and these follicles are formed by central cavity filled with sticky fluid known as colloid. The colloid is the center of thyroid hormone production that is surrounded by a wall of epithelial cells. Colloid is dependent upon iodine; the most important component and mediator for thyroid hormone production which is obtained from diet.

Thyroid gland produces mainly two hormones; thyroxin (T4) and triodothyronin (T3) which are controlled by thyroid stimulating hormone (TSH) secreted from anterior pituitary gland. Thyroid follicular cells produces thyroglobulin, the pre-cursor of T4 and T3 before being secreted and stored in the follicular lumen. Iodine is an essential trace element absorbed in the small intestine which is an integral part of T3 and T4. Iodide is actively absorbed from the bloodstream by the process called iodide trapping.

Monoiodotyrosine (MIT) and diiodotyrosine (DIT) is formed through a reaction with the enzyme thyroperoxidase, iodine is bound to tyrosine residues in the thyroglobulin molecules. T3 is produced from the combination of one particle of MIT and one particle of DIT whereas association of two DIT molecules produces T4. When TSH stimulates its receptor, the processed thyroglobulin molecule is endocytosed within the follicular cell and is further acted on by lysosomes, releasing the T4 and T3 molecules into circulation. T4 is said to be a pro-hormone and reservoir for main hormone T3 which is more active form. T4 is converted as required in the tissue by iodothyronine deiodinase.[12,13]

ETIOLOGY OF THYROID DISORDERS

The different factors like heredity, inadequate levels of dietary iodine intake, pregnancy, radiotherapy, viral infection, surgery, underlying disease such as infiltrative disorders or auto immunity are responsible for development of endocrine diseases of thyroid which may be expressed as under or over activity of the gland.[14,15]

Hypothyroidism and Subclinical hypothyroidism share the common etiologies.[16] Worldwide iodine deficiency is regarded as the most common cause of hypothyroidism. Though SCH carries various causing factors, the most common (60% to 80%) cause of sub clinical hypothyroidism is Chronic autoimmune thyroiditis which is associated with the presence of anti-thyroid peroxidase antibodies, a marker of chronic lymphocytic (Hashimoto's) thyroiditis.[1] In the studies it is suggested that Hashimoto's thyroiditis is more prevalent in girls and women, but the overall incidence increases with age in both sexes. Other various causes of sub clinical hypothyroidism involves inappropriate substitution treatment for the manifested thyroid insufficiency, low compliance with treatment, inappropriate monitoring of treatment, drug interaction, persons with autoimmune thyroidism and high titre of thyroid auto antibodies.[17] Genetics also plays a role for TSH elevation in subclinical hypothyroidism.[18] Other risk factors including female sex, older age, goiter, neck irradiation or radioactive iodine exposure, and high iodine intake leads to development of hypothyroidism.[19,20]

Subclinical hypothyroidism is a common disorder which may represent "early" thyroid failure. It may occur in the presence or absence of symptoms.[21] When TSH levels are mildly elevated then the symptoms like depression, constipation, fatigue, goiter, weight gain, hair loss, intolerance to cold, memory problem with brain fog may arise.

EPIDEMIOLOGY

About 40 years ago Evered et al, proposed the gradation of hypothyroidism along biochemical criteria, which is classified accordingly between grade I (subclinical), grade II (mild), and grade III (overt) hypothyroidism as mentioned below.[22]

Hypothyroidism grade IA : TSH- increased, >4.0 to <10 mU/l, FT4- normal, FT3- normal

Hypothyroidism grade IB : TSH increased, >10 mU/l, FT4- normal, FT3- normal

Hypothyroidism grade II : TSH increased, FT4- decreased, FT3- normal

Hypothyroidism grade III : TSH increased, FT4- decreased, FT3- decreased

The global prevalence ranging from 1 to 10% of the adult population with increasing frequency in women, in patients with advanced age, and in those with greater dietary iodine intake.[21] The prevalence of SCH in the population varies from 4 to 20%, occurring more frequently in adults older than 65 years of age.[23] In Another study prevalence of subclinical hypothyroidism was observed 17.0%. Out of the total Subclinical hypothyroidism cases 23.1% were seen in less than 15 year of age group and the decreasing trends of prevalence was seen with increasing age.[24]

Similarly a study from north Indian population interpreted, significant prevalence of subclinical hypothyroidism in which females are found to be more affected than males and the condition is seen more common in younger age group which is in contradiction to the previous studies where subclinical has been found to be more common with advancing age.[25,26] In a recent study using Korean population-based cohorts, the prevalence of SCH was reported to be 11.3%.[27] The prevalence of SCH is relatively high in the adult population with women, elderly people, and iodine-sufficient populations being affected more often and ranges from 4% to 20%.[28]

Prevalence of Subclinical hypothyroid patients was 14% in the age group of 20-39 years with 55.40% prevalence in the total population among the total thyroid disorders and 3.58% participants with subclinical hypothyroidism were habitual to smoking ,out of 18% smokers among the study population. Probably, the mechanism to synthesize free radicals may be related with the smoking habits and thyroid dysfunctions.[29] Similar findings were reported by two studies which was conducted in Nepal[30] , few more studies also observed the similar results.[31,32,33] Though, The effect of subclinical hypothyroidism (SCH) on hyperlipidemia is not so much clear.[34,35,36]

Subclinical hypothyroidism (SCH) might be a secondary cause of hyperlipidemia and hence related to coronary heart disease (CHD) has been suggested by a retrospective cohort study done to observe thyroid functioning of 8795 patients of different races with newly diagnosed hyperlipidemia; TSH was found to be high in 5.2% of the 49.5% of patients who were diagnosed with hyperlipidemia. Particularly, 3.5% had a TSH level of 5 to 10 mIU/L and 1.7% had a TSH level >10 mIU/L. The patients with TSH values between 5.1 and 10 mIU/L have significantly higher mean total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) levels as compared to euthyroid subjects, shows rise in lipid levels, as thyroid function declines.[37] A meta-analysis of 55 cohort studies with 1,898,314 patients

demonstrated/ interpreted that subclinical and overt hypothyroidism were associated with higher risks of cardiac mortality and all-cause mortality. The same study also reported that hypothyroidism is a risk factor for Ischemic heart disease (IHD) and associated with higher risks of cardiac mortality and all-cause mortality compared with euthyroidism in the general public or in patients with cardiac disease.[38]

The negative impact of sub clinical hypothyroidism in terms of heart or cardiovascular (CV) risk is recognized in young adults of <55-60 years, is found still controversial in the elderly age group of >65 years, especially in the oldest old (aged 80 year).[39]

THYROID HORMONE AND LIPID METABOLISM

THs are mainly bound to specific proteins in the blood, that transfer them through the circulation; only a small part of THs is free and exerts its action on target tissues. In the lipid metabolism, thyroid hormone is regarded as main regulator of lipid metabolism by stimulating the mobilization and degradation of lipids as well as *de novo* fatty acid synthesis in the liver.[40] Thyroid hormones induce the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the first step in cholesterol biosynthesis.[41] The cholesterol is formed in the liver and is transferred through the circulation by lipoproteins, which are classified according to their size and density. The plasma concentration of cholesterol is reduced through T3 and some THs mimetic compounds, by inducing its hepatic uptake and conversion into bile acids and by favouring faecal bile acid excretion.[42,43]

Concentration of cholesterol in plasma is decreased by T3 and some compounds with similar effects like THs on cholesterol metabolism. These compounds promote hepatic intake of cholesterol and its conversion into bile acids and by favouring faecal bile acid excretion.[42,43] Different forms of thyroid dysfunctions whether overt, subclinical or hypothyroidism, adversely effects metabolism of lipids which causes increased level of cholesterol in blood, further amplify the risk for cardiovascular disease and, undoubtedly, mortality. Activity of low-density lipoprotein (LDL) receptor decreases in hypothyroidism which causes hypercholesterolemia simultaneously there is diminished control of T3 on sterol regulatory element-binding protein 2 (SREBP-2) occurs. These processes bring out changes in cholesterol biosynthesis by regulating rate-limit degrading enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) activity.[44]

Lipolysis from fat stores in white adipose tissue and from dietary fat sources is stimulated by thyroid hormones and converts fat in to free fatty acids (FFAs), which are the major source of lipids for the liver. Protein transporters mainly fatty acid transporter proteins (FATPs), liver fatty acid binding proteins (L-FABPs) and fatty acid translocase (FAT; also known as CD36) play important role transportation of FFAs into hepatocytes.[45] SREBP2 is a key transcription factor that induces the expression of lipogenic-related genes, including *Ldlr*.[46] Levels of very-low-density lipoprotein (VLDL) in the liver and in serum are influenced by lipoprotein lipases that are up-regulated by thyroid hormones.[47] since the LDL-receptor and the sterol regulatory element-binding protein 2 (SREBP2) are under-expressed in hypothyroidism, Low-density lipoprotein (LDL) accumulates in the serum of hypothyroid patients. In addition, ApoB100 levels are reduced by THs contributing to the increase in VLDL and LDL production observed in the liver during hypothyroidism.[48]

Thyroid hormones regulate the expression of many of the genes involved in lipogenesis by binding to their specific THR.[49-52] However, in addition to regulating lipogenic gene expression directly, thyroid hormones also indirectly control the transcriptional regulation of hepatic lipogenesis as a result of their effects on the expression and activities of other transcription factors, such as sterol regulatory element- binding protein 1C (SREBP1C), liver X receptors (LXRs) and carbohydrate-responsive element-binding protein (ChREBP), which all have crucial roles in hepatic lipogenesis.[53] Thyroid hormones directly induce the gene expression of the LXRs[54] and ChREBP[55] in hepatic cells via the recruitment of THRs to the promoters of these genes. Thyroid hormones stimulate the utilization of lipid substrates owing to an increased mobilization of triglycerids stored in adipose tissue. Increased concentrations and appearance rates of plasma non-esterified fatty acids (NEFA) and glycerol reflect this action. The mechanisms of thyroid hormone action on lipolysis remain unclear. No direct lipolytic effect has been found in vitro. The increased lipolytic rate produced by thyroid hormones in vivo might be related to the increased subcutaneous blood flow or to a modification of the lipolytic action of catecholamines.[56]

Thyroid hormone influence HDL metabolism probably by increasing cholesteryl ester transfer protein (CETP) activity, that replaces cholesteryl esters from HDL_2 to the very low density lipoproteins (VLDL) and TGs to the opposite direction.[57] Thyroid hormones stimulate the lipoprotein lipase (LPL) as well, which catabolizes the TG-rich lipoproteins, and the hepatic lipase (HL), which hydrolyzes HDL_2 to HDL_3 and contributes to the

transformation of intermediate-density lipoproteins (IDL) to LDL and in turn LDL to small dense LDL (sdLDL).[58,59]

Furthermore, the effect of T_3 is the up-regulation of apolipoprotein AV (ApoAV), which plays an important role in TG regulation[60] and decreased levels of TGs have been associated with increased levels of ApoAV.[61]

De novo lipogenesis (DNL) is a complex and highly regulated process in which carbohydrates from circulation are converted into fatty acids that are then used for synthesizing either triglycerides or other lipid molecules.[62] THs stimulate the de novo fatty acid synthesis (de novo lipogenesis, DNL), through both the modulation of gene expression and the rapid activation of cell signalling pathways.[63] T_3 has also been associated with protecting LDL from oxidation.[64] Triiodothyronine (T_3) and triiodothyroacetic acid (TA_3) are thyroid compounds that similarly protect low-density lipoprotein (LDL) against oxidation induced by the free radical generator 2,2′-azobis-[2-amidinopropane] dihydrochloride (AAPH).[65]

LIPID ALTERATION IN SUB CLINICAL HYPOTHYROIDISM

Thyroid hormone causes numerous effects on the regulation, absorption, and metabolism of lipid synthesis[66] as it regulates cholesteryl-ester transfer protein (CETP) and hepatic lipase (HL), both are decreased due to high-density lipoprotein (HDL) levels which are normal or even elevated in severe hypothyroidism.[67] Although the relationships between SH and lipid profile have been reported in different studies but the result seems conflicting. Several studies found serum LDL-C levels increased in SCH patients[68,69,70] whereas some reported higher serum total cholesterol levels in SCH patients[71,72] and other studies reported lower serum TC level.[73]

In a large cross-sectional study thyroid clinic outpatients, total cholesterol and LDL-C were clearly elevated in overtly hypothyroid patients, but there were no significant differences in serum total cholesterol, LDL-C, HDL-C, or triglyceride levels between subclinically hypothyroid patients and the euthyroid groups.[74]

Various studies have shown that SCH associated with hyperlidemia.[75,76,77,78] The serum triglyceride levels more than 160 and <200 mg/dl showed significant % prevalence for TSH levels <10[79, 81] and atherogenic lipid profile noted in Indian population with TSH >10

mIU/ml.[81] In a population based study from north India in age group of 15- 65 years with SCH a significant elevation in serum triglyceride & VLDL levels are observed and no significant change was found in the lipid fraction with severity of SCH.[80] The status of patients with altered lipid parameters are observed in cases whose TSH levels are <10 mIU/ml is revealed from a study of south India. The clinical hypothyroidism is shown to have increase of lipid parameters with positive correlation in these patients.[82]

A number of studies have reported significant increases in serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and total triglyceride levels (TG) in patien ts with SCH and the findings of a meta-analysis suggested that the TC, LDL-C, and TG levels of SCH subjects are significantly increased as compared to euthyroid individuals.[83] Similarly, in the previous study on prevalence of SCH in eastern region of Nepal, concluded 20.42% ,of which the highest percentage was found in the female age group 20 – 59 years and with increasing age in hypothyroid and sub-clinical hypothyroid subjects, increased level of total Cholesterol was observed.[84,85]

BLOOD PRESSURE AND SUB CLINICAL HYPOTHYROIDISM

As, both hypothyroidism and hyperthyroidism are considered to increase the risk of hypertension. Though, there is still controversial relationship between subclinical hypothyroidism and blood pressure.[86]

Thyroid hormone plays a significant role in normal functioning of cardiovascular system but its alteration contributes to assist cardiovascular risk. Overt hypothyroidism is associated with increased systemic vascular resistance (SVR), decreased cardiac contractility, and decreased cardiac output.[87] Sub clinical hypothyroidism can raise the levels of blood pressure. The mechanism responsible for the increased blood pressure level in clinical hypothyroidism patients could be the rise of systemic vascular resistance.T3 can cause vasodilation by directly acting on smooth muscle cells of blood vessel.[86] Hence decreased T3 level in hypothyroidism, increases the vascular resistance and the level of blood pressure. Hypothyroidism can also lead to the abnormality of sodium metabolism, the raised sympathetic nervous system activity, and the decreased glomerular filtration rate etc., which may be associated in the manifestation of hypertension.[87,88,89]

Moreover, an increasing amount of evidence indicates that higher levels of TSH are correlated with worsening blood pressure (BP) and altered lipid levels. A cross-sectional

study investigated that subjects with SCH exhibit increased BP.[90] An association between subclinical hypothyroidism and hypertension has been verified by some, but not all studies. Similarly, a recent meta-analysis found that SCH is associated with slightly higher systolic BP.[91] A population-based study observed positive linear associations between TSH levels and systolic / diastolic BP that may have long-term implications for cardiovascular health.[92] Some studies reported higher DBP, or higher prevalence of hypertension in SCH subjects,[93,94] whereas others reported no association of SCH and hypertension.[95,96,97] It has been argued that in the hypothyroid state, the sympathetic and the renin-angiotensin-aldosterone systems are possibly implicated in the homeostasis of arterial pressure.[98,99]

HEART FAILURE AND SCH

Heart Failure (HF) is growing in developed and developing countries at a great rate, with an estimated prevalence of more than 37 million individuals[100] and is a frequent cause of hospitalization in people >65 years of age, with an increasing trend in the number of patients living with HF.[101,102] Usually patients with overt hypothyroidism are reported to have Lipid abnormalities and changes in lipid profile is supposed to contribute to the disproportionate increase in cardiovascular risk in those persons. SCH is found to be associated with lipid disorders, characterized by normal or slightly elevated total cholesterol, increased LDL and lower HDL. SCH is also associated with endothelial dysfunction, aortic atherosclerosis and myocardial infarction.[103,104,105] Yet, sub clinical hypothyroidism permits life-long thyroxine replacement therapy or not, it remains still controversial.

Subclinical hypothyroidism can affect the cardiovascular system by increasing heart rate, and severe left ventricular dysfunction.[106,107] It is reported that patients with a thyroid-stimulating hormone (TSH) level > 10 mIU/L have a elevated risk of developing heart failure with reduced ejection fraction as compared to subjects with normal thyroid function. The potential mechanisms responsible for diastolic dysfunction of the left ventricle (LV) in SCH are connected with endothelial dysfunction and arterial stiffness, inflammatory state and are driven by TSH apoptosis-derived microparticles.[108] A large prospective cohort study with 25,378 participants interpreted/found that the risk of HF increased both with lower and higher TSH levels, especially in those with TSH levels ≥10.0 mIU/L and in those with TSH <0.10 mIU/L.[109]

CARDIOVASCULAR DISEASE AND MORTALITY

The layer that lines the internal surface of blood vessels (arteries, veins and capillaries) and lymphatic vessels and the heart is termed as endothelium. The endothelium plays a role in vascular homeostasis and has many endocrine, autocrine and paracrine functions,[110] which is important for synthesizing vasoconstrictor and vasodilator substances.[111]

Endothelial dysfunction is a disproportion between vasodilation and vasoconstriction, and is related to atherosclerosis and cardiovascular events.[112] Though, the correlation between sub clinical hypothyroidism and cardiovascular disease is still controversial, there may have an adverse impact on the cardio vascular system due to little changes in Thyroid hormone concentration and subclinical thyroid dysfunction has been associated with a 20% to 80% increase in vascular morbidity and mortality risk.[1,113,114] Cardiovascular disease accounts for the largest share of mortality in developed nations and increasing gradually in developing countries. Numerous studies have shown the negative effect of overt hypothyroidism on factors contributing to cardiac health such as, body mass index (BMI), lipid profile, blood pressure, endothelial function and left ventricular function.[115]

SCH has been associated with increased risk of CHD, supported by several studies and meta-analyses which have revealed the association of SCH with CV risk and mortality.[116,117] A high risk of coronary heart disease (CHD) events and mortality was reported in dependency on the degree of TSH, with lower risk of all-cause mortality in SCH patients having a TSH between 5–10 mU/l, and also in subjects younger than 65 years.[118] A cohort study from Rotterdam showed that subclinical hypothyroidism in women older than 55 years with serum TSH levels between 4 and 10 mIU/L is a strong risk factor, independent of cholesterol level, for atherosclerotic disease and myocardial infarction.[119]

According to another meta-analysis, SCH is associated with a significant risk of CHD at baseline as well as at follow-up, though there is a significant difference between the relative risk of CHD in two catagories i.e. (RR with 95 % CI 1.533 [1.312–1.791]; $p<0.05$) and at follow-up (RR with 95 % CI 1.188 [1.024–1.379]; $p<0.05$). The same study concluded that mortality from cardiovascular causes is significantly higher at follow-up.[120] A large prospective study involving an elderly population (>85 years) noted an association between grade 1 subclinical hypothyroidism and decreased all-cause mortality.[121] The higher cardiovascular mortality rates in group 2 subclinical hypothyroidism patients are related to known cardiovascular effects of thyroxine on heart function and metabolism. Cardiovascular

alterations that occur in overt hypothyroidism have also been identified in subclinical hypothyroidism, effects varying only in the degree of derangement.[122]

Similarly, in a Taiwanese 10-year follow-up study it was observed that 11,574 participants without a history of thyroid disease in which SCH was defined as a serum TSH level of 5.0–19.96 mU/l with normal fT4 concentrations, 680 out of 3,669 deaths were due to CVD. Compared with subjects with euthyroidism, after adjustment for age, sex, body mass index, diabetes, hypertension, dyslipidemia, smoking, alcohol consumption, betel nut chewing, physical activity, income, and education level, the relative risk (95% confidence interval) of deaths from all-cause and CVD among subjects with SCH were 1.30 (1.02 to 1.66), and 1.68 (1.02 to 2.76), respectively and adult Taiwanese with SCH had an increased risk for all-cause mortality and CVD death has found.[123]

TREATMENT

Children and adolescents, pregnant women, and women contemplating pregnancy should receive treatment. Thyroxine therapy helps improvement patient from worsening of their lipid profile. T4 treatment in women with sub clinical hypothyroidism (TSH values >2.5mU/L) who are pregnant, who wish to become pregnant, or have ovulatory dysfunction and infertility is recommended.[124] A double blinded randomized control trial reported significant improvement in symptomatic patients with sub clinical hypothyroidism treated with levothyroxine compared with placebo.[125]

The two different randomized control trials confined to individuals with TSH levels lower than 10mIU/L found no improvement in symptoms with levothyroxine therapy.[126,127] Usually when the TSH level is >10.0 mIU/I, levothyroxine treatment is recommended. For patients having TSH <10.0 mIU/L (mild-SCH) adverse events and benefits of treatment remains controversial and there is still no concordance regarding its clinical importance.[128] Patients should be reviewed 3–4 months after normalization of TSH and if there is no improvement in symptoms then treatment should be stopped in patients having mild-TSH (<10 mIU/l) who have started on treatment mainly due to symptoms.[129]

Improvement of diastolic function, positive effect on systolic function, and increase in ejection fraction has been found by T4 therapy which can be taken as an evidence in favour of the theory that T4 treatment improves lipid and cardiac abnormality.[130] Synthetic T4 is the treatment of choice for replacement of hypothyroidism. For older person and those with

associated CVD, the starting dose of T4 is usually 25-50 mcg/day.[124] In a double-blind, randomized, placebo-controlled, parallel-group trial including 737 adults who were at least 65 years of age and who had obtaining sub clinical hypothyroidism (thyrotropin level, 4.60-19.99 mIU/L; free thyroxine level within the reference range). Sub clinical hypothyroidism provided no probable benefits in old aged people taking levothyroxine treatment was concluded.[131]

CONCLUSION

By co-relating subclinical hypothyroidism and cardiovascular risk factors from different evidence and studies it is interpreted that subclinical hypothyroidism leads to lipid disorder which plays significant role for cardiovascular malfunction. In general, it is observed that higher levels of TSH are correlated with worsening blood pressure. Similarly, most of the studies concluded that thyroid hormone has various effects on lipid alteration. This study observed that in the subclinical hypothyroidism TSH level is higher than in euthyroid subjects. Though, subclinical hypothyroidism is a syndrome not a disease.

In this review, the impact of SCH in CVS is studied but further more investigation is required for preventive recommendations of CV risk. However, we still found controversy between different authors in their studies about the necessity for treatment of SCH.

In summary, it is interpreted that alteration of thyroid hormone may contribute risk for development of cardio vascular disease and mortality.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Abbreviations

SCH	Sub clinical Hypothyroidism
TSH	Thyroid Stimulating Hormone
CVD	Cardio vascular Disease
TG	Triglyceride
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
MIT	Monoiodotyrosine
DIT	Diiodotyrosine
TC	Total Cholesterol
IHD	Ischemic heart disease
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
SREBP-2	Sterol regulatory element-binding protein 2
FFAs	Free fatty acids
CETP	Cholesteryl-ester transfer protein
VLDL	Very low density lipoprotein
ChREBP	Carbohydrate-responsive element-binding protein
SREBP1C	Sterol regulatory element- binding protein 1C
NEFA	Non-esterified fatty acids
LPL	Lipoprotein lipase
HL	Hepatic Lipase
DNL	*De novo* lipogenesis
TA_3	Triiodothyroacetic acid
SVR	Systemic vascular resistance
CHD	Coronary heart disease