

## Association between Subclinical Hypothyroidism and Dyslipidemia

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### Original Research Article

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**Abstract:** Subclinical hypothyroidism (SCH) may be associated with increased risk of Coronary Artery Disease and various biochemical abnormalities like dyslipidemia, increased LDL-C levels, increased total cholesterol and serum triglyceride values. The present study was aimed to determine lipid abnormalities in patients with subclinical hypothyroidism and its association with thyroid profile. The present case control study was conducted in 50 patients aged from 18 to 65 years (25 subclinical hypothyroidism cases and 25 euthyroid controls. T<sub>3</sub>, T<sub>4</sub>, TSH was assessed by using semi-automated Chemiluminescence immunoassay, lipid profile was done using autoanalyzer. Data was analysed using SPS SOFTWARE. The mean Cholesterol levels (276.1±73.56), mean LDL-cholesterol levels (191.7 ±72.5), mean triglyceride levels (156.64±45.38) were increased in Sub Clinical Hypothyroidism cases compared to control groups. Our study shows that TSH levels were positively correlated with cholesterol, LDL and negatively with HDL in patients with Subclinical hypothyroidism.

**Keywords:** subclinical hypothyroid, lipid profile, TSH.

### INTRODUCTION

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone, in which the thyroid gland produces insufficient amounts of thyroid hormone total thyroxine T<sub>4</sub> and triiodothyronine T<sub>3</sub>. It can also be secondary to lack of thyroid hormone secretion due to inadequate secretion of TSH by pituitary or TRH from hypothalamus. Decrease in T<sub>4</sub> and T<sub>3</sub> leads to hyperfunctioning of pituitary and increase in TSH levels.

Subclinical hypothyroidism is defined as elevated serum thyroid stimulating hormone (TSH) concentration in the presence of normal circulating thyroid hormones triiodothyronine (T<sub>3</sub>) and total thyroxine (T<sub>4</sub>). Patients with subclinical thyroid disease have a few or no symptoms or signs of thyroid dysfunction and thus subclinical thyroid disease is diagnosed by laboratory findings [2]. The prevalence of subclinical hypothyroidism is about 4 to 8.5 percent, and may be as high as 20 percent in women older than 60 years [1]. Hypothyroidism is associated with elevated cholesterol and low density lipoprotein levels, a relation that has been well established for more than 50 years [70].

Although the impacts of overt hypothyroidism on metabolic functions are well documented [71], the metabolic effects of subclinical hypothyroidism remain controversial. Studies have reported that cholesterol levels were significantly elevated in subclinical hypothyroidism [57], but other reports, could not find changes in lipid profile in patient with subclinical hypothyroidism [72].

Biochemical screening for thyroid dysfunction is of paramount importance in all dyslipidemia patients, as well as in all unexpected improvement or worsening of their lipid profile. Underlying thyroid disorders should be recognized and treated in this setting. There is an absolute need for study design to answer the question as to whether subclinical hypothyroidism is associated with dyslipidemia that might influence cardiovascular morbidity and mortality.

So, our study is designed to find the association between subclinical hypothyroidism and dyslipidemia in the local population attending Tertiary Care Hospital.

### Objectives of the study

- To find out the association between subclinical hypothyroidism and dyslipidemia by estimating the values of thyroid profile and values of lipid profile in subclinical hypothyroid patients
- To compare them with the controls

### REVIEW OF LITERATURE

Subclinical Hypothyroidism is a mild thyroid gland dysfunction, with or without symptoms of hypothyroidism. It is diagnosed biochemically by elevated serum Thyrotropin (TSH) level with normal serum triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>).

Subclinical Hypothyroidism is a frequently observed biochemical abnormality [1-3]. Currently, the most widely accepted interpretation of the biochemical findings in SCH is that the increased TSH is an indication of mild hypothyroidism (HYPO) with a slightly reduced peripheral thyroid hormone effect. The causes of SCH resemble the causes of HYPO; Progression of SCH to HYPO is in the order of 5–8%/year. Normalisation of thyroid function is another possible outcome, and many patients have stable SCH and do not experience systematic deterioration in thyroid function for years [4].

Although SCH may resolve or remain stable for years, in some patients' overt hypothyroidism develops with decreased T<sub>3</sub> and T<sub>4</sub> levels and increased TSH levels. The likelihood of overt hypothyroidism to occur increases with greater TSH elevations and presence of antithyroid antibodies.

Because SCH may be associated with increased risk of coronary artery disease (CAD), peripheral vascular disease, and various biochemical abnormalities persistent and definite TSH elevations should be considered for thyroid treatment [5].

With the invention of TSH radioimmunoassay in the 1970s, mildly increased TSH levels and normal thyroid hormone levels was detected. With further introduction of more sensitive TSH radioimmunoassay in 1980s subclinical hyperthyroidism where TSH is decreased and thyroid hormones were normal was identified. Subclinical hypothyroidism can only be diagnosed based on test results [6]. Much attention has been focused on this clinical entity recently, but it remains controversial whether early thyroid replacement therapy improves outcomes in patients with asymptomatic subclinical hypothyroidism [7].

### Thyroid gland and its hormones

The thyroid gland is present in the neck below the thyroid cartilage. The normal adult thyroid gland consists of two lobes connected by an isthmus [8]. It is the largest endocrine organ, and is essential to mammalian life. The thyroid gland produces two related hormones, thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>). Acting through nuclear receptors, these hormones play a critical role in cell differentiation during development and help to maintain thermogenic and metabolic homeostasis in the adult.

Thyroid stimulating hormone (TSH) secreted by the thyrotrope cells of the anterior pituitary, is a 31kDa hormone composed of  $\alpha$  and  $\beta$  subunits. The thyroid axis is a classic example of an endocrine feedback loop. Hypothalamic TRH stimulates pituitary production of TSH, which, in turn, stimulates thyroid hormone synthesis and secretion. Thyroid hormones negatively feedback to inhibit TRH and TSH production (Figure 1). The "set-point" in this axis is established by TSH, the level of which is a sensitive and specific marker of thyroid function. TRH is the major positive regulator of TSH synthesis and secretion. TRH acts through a seven transmembrane G protein-coupled receptor (GPCR) that activate phospholipase C to generate phosphatidylinositol turnover and the release of intracellular calcium.

T<sub>3</sub> and T<sub>4</sub> are derived from Tg, a large iodinated glycoprotein. After secretion into the thyroid follicle, Tg is iodinated on selected tyrosine residues that are subsequently coupled via an ether linkage. Reuptake of Tg into the thyroid follicular cell initiates proteolysis and the release of newly synthesized T<sub>4</sub> and T<sub>3</sub>. Iodide uptake is a critical first step in thyroid hormone synthesis.

Iodide uptake is mediated by the Na/I symporter (NIS), which is expressed at the basolateral membrane of thyroid follicular cells. After iodide enters the thyroid, it is trapped and transported to the apical membrane of thyroid follicular cells where it is oxidized in an organification reaction that involves thyroid peroxidase (TPO) and hydrogen peroxide. The reactive iodine atom is added to selected tyrosyl residues within Tg, a large (660 kDa) dimeric protein that consists of 2769 amino acids. The iodotyrosines in Tg are then coupled via an ether linkage in a reaction that is also catalyzed by TPO. Either T<sub>4</sub> or T<sub>3</sub> can be produced by this reaction, depending on the number of iodine atoms present in the iodotyrosines. After coupling, Tg is taken back into the thyroid cell where it is processed in lysosomes to release T<sub>4</sub> and T<sub>3</sub>. Uncoupled mono- and diiodotyrosines (MIT, DIT) are deiodinated by the enzyme dehalogenase, thereby

recycling any iodide that is not converted into thyroid hormones.

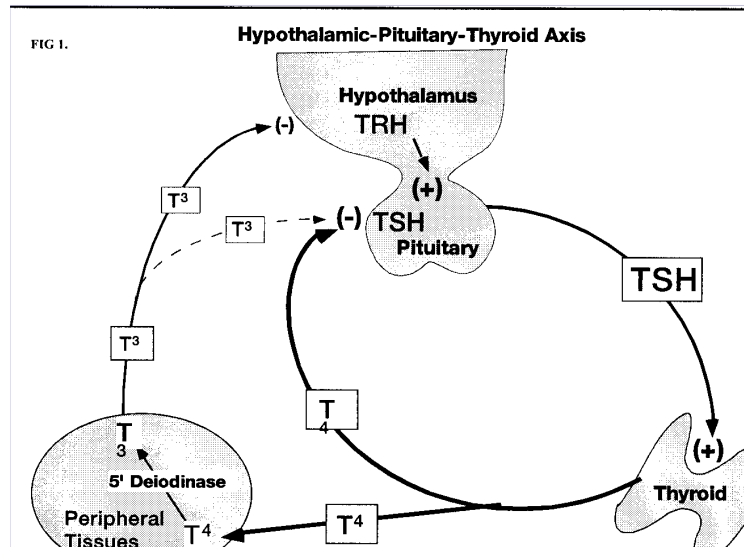


Fig-1: Regulation of thyroid hormones

T4 is secreted from the thyroid gland in at least 20-fold excess over T3. Both hormones circulate bound to plasma proteins, including thyroxine binding globulin (TBG), transthyretin (TTR, formerly known as thyroxine-binding prealbumin, or TBPA), and albumin. About 80% of T4 is metabolised by deiodination, 35% to T3 and 45% to reverse T3 (rT3). The remainder is inactivated mostly by glucuronidation in the liver and secretion into bile, or to a lesser extent by sulfonation and deiodination in the liver or kidney.

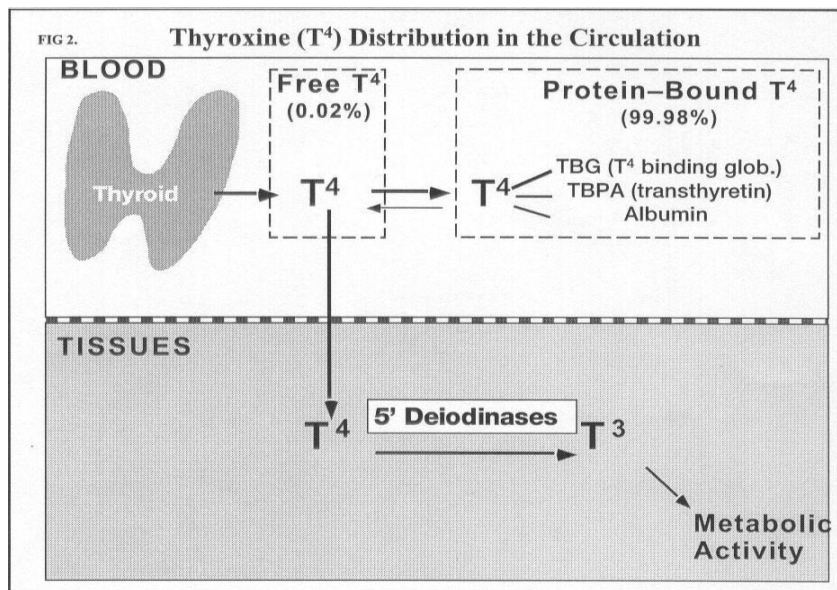


Fig-2: thyroid hormone transport

**Global prevalence**

About 5% of U.S. adults reported to have thyroid disease or they take thyroid medication [9, 10]. In a cross-sectional study of 2,799 well-functioning adults 5.6% to 16.5% reported to have hypothyroidism [11]. The prevalence of SCH was 1.8% to 5.6%. Older age and female sex are proved risk factors for SCH. In the NHANES-III survey, the overall prevalence of a serum TSH  $\geq 4.5$  mU/l was about 2% -8%. In a population-based study in Whickham, England, the prevalence was 4% to 5% in women age 18 to 44[12]. Different studies give various TSH ranges. The progression of SCH to overt hypothyroidism is approximately 2% -5% per year. The progression to overt hypothyroidism mainly depends on the baseline TSH concentration and is relatively higher in subjects with antithyroid antibodies.

**Prevalence in India**

In India the prevalence of thyroid diseases is significant. Thyroid diseases are one among the commonest endocrine diseases in India. According to a projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from thyroid diseases [13]. In Cochin, Kerala a population-based study on 971 adult subjects, the prevalence of hypothyroidism was found to be 3.9%. The prevalence of SCH was high in this study<sup>14</sup>, the value being 9.4%. The prevalence of SCH increases with age [13]. Almost 53% of subjects with SCH were positive for anti-TPO antibodies. Urinary Iodine Status was studied in 954 subjects from the same population sampled, and the median value was 211 µg/l; this suggested that this population was iodine sufficient [13].

**Natural history and prevalence**

Many population based study have suggested that prevalence of SCH increases with age and it is comparatively higher among women than men. The worldwide prevalence of SCH ranges from 1 to 10 %; the highest age- and sex-specific rates are in women older than 60 years of age, approaching 20 % in some reports [15]. In the Whickham, UK survey it was found that serum TSH levels did not vary with age in men but it increased markedly in women aged greater than 45 years[12]. There was a high prevalence of SCH in the elderly in a geriatric ward in a restructured hospital [16]. Increased TSH levels have strong association with positive antithyroid antibodies. The prevalence of increased TSH levels parallels that of antibody positivity [17]. Anti-thyroid antibodies were found in 60% of those with high TSH and normal thyroid hormones but only 5.6% of those with subnormal TSH [18].

Serum TPOAb and TgAb concentrations increased with age. Antibodies were more prevalent in women than in men. Increasing serum thyroid antibody prevalence with age has been found in other studies [19]. In the Wickham survey, after a period of twenty years the risk of overt hypothyroidism was found to be 4.3% per year in women with increased TSH and antithyroid antibodies at baseline. Elevated TSH or presence of antithyroid antibodies alone at baseline also conferred an increased risk of overt hypothyroidism [20]. Progression to overt hypothyroidism from SCH was noted to be more common in those with initial TSH value more than 10mU/l and in those with positive antithyroid antibodies [21].

In a study in Europe, authors found the risk factors such as degree of TSH elevation, decreased thyroid reserve and the presence of microsomal (thyroperoxidase) antibodies can identify patients with SCH at greatest risk for progression to overt hypothyroidism, mainly patients with TSH levels greater than 10 mU/l [22].

**Table-1: Causes of hypothyroidism**

<p><b>HEREDITARY /CONGENITAL</b>                  Enzyme deficiency affecting thyroid hormone biosynthesis                  Agenesis                  Hormone Resistance                  Endemic Cretinism</p>
<p><b>HYPOTHALMIC –PITUTARY DISORDERS</b>                  Thyrotropin- releasing hormone deficiency                  Thyroid- stimulating hormone deficiency</p>
<p><b>DESTRUCTIVE</b>                  Postoperative                  Radio-active iodine                  External Radiation to neck                  Infiltrative diseases</p>
<p><b>AUTOIMMUNE</b>                  Hashimoto’s Disease                  Grave’s Disease</p>
<p><b>THYROIDITIS</b>                  Subacute                  Silent                  Postportum</p>
<p><b>DRUG-INDUCED</b>                  Iodides                  Lithium                  Thionamides</p>
<p><b>IDIOPATHIC</b></p>

**Causes of subclinical hypothyroidism**

The causative factors for SCH are same as for hypothyroidism. Most common cause include chronic autoimmune thyroiditis (Hashimotos disease), in which antithyroid antibodies, such as antimicrosomal antibodies and antithyroglobulin antibodies [21]. Radioiodine or surgical treatment of Grave’s thyrotoxicosis is another major cause of SCH. Several drugs, specially iodine and iodine containing drugs, amiodarone and lithium cause SCH. External radiation may cause SCH<sup>23</sup>. Pituitary failure is a cause of secondary hypothyroidism but the TSH level is low rather than high, this condition cannot be diagnosed with certainty until thyroid hormone levels fall below normal, and SCH would not be detected.

The elevated TSH level in SCH will be normal if measured again several months later; we would then attribute the initial elevation to laboratory error or, perhaps, to an episode of silent thyroiditis with a transient hypothyroid phase. In other cases, the SCH remains unchanged. The third possibility, progression to overt hypothyroidism, occurs at a rate of about 5 percent per year in patients with raised TSH levels and detectable antithyroid antibodies [24]. In selected cases (e.g., elderly patients with high titers of antithyroid antibodies), the risk of progression to overt disease may be closer to 20 percent per year [25].

**Signs and symptoms**

The clinical signs and symptoms of hypothyroidism manifest only when the disease is fully developed. But in SCH, one or more of these findings may occur. In one study, symptoms in 33 patients with SCH were compared with symptoms in 20 euthyroid patients in the same thyroid clinic. Dry skin, cold intolerance and easy fatigability were significantly more common in the patients with raised TSH levels, and these symptoms improved after treatment with thyroid hormone <sup>26</sup>. In another study of 69 female patients with SCH, a clinical index based on symptoms and physical signs were shown to be more abnormal in patients with higher TSH levels, even though all patients had normal serum levels of T4 and free T4. These studies suggest that some patients with SCH do indeed have clinical manifestations of mild thyroid failure [27].

**Table-2: Clinical findings in hypothyroidism**

Affected areas	Symptoms	Signs
General	Cold intolerance Fatigue Mild weight gain	Hypothermia
Nervous system	Lethargy Memory defects Poor attention span Personality change	Somnolence Slow speech Myxoedema wit Psychopathology Myxoedema madness Diminished hearing and taste Cerebellac ataxia
Neuromuscular system	Weakness Muscle cramps Joint pain	Delayed relaxation of deep tendon reflexes
Gatrointestinal system	Nausea Constipation	Large tongue Ascitis
Cardiorespiratory system	Decrease exercise tolerance	Hoarse voice Bradycardia Mild hypertension Pericardial effusion
Preproductive system	Decreased libido Decreased fertility Menstrual disorders	
Skin and appendages	Dry, cough, skin Puffy faces Hair loss Brittle nails	Nonpitting, oedema of hands, face, and ankles Periorbital swelling Pallor Yellowish skin i.e. Carotenemia Coarse hair Dry axillae

### **Lipid alterations in thyroid disease**

It is universally accepted that there is a correlation of lipid profile alteration among hypothyroidism patients. There were also documented studies, on whether the dyslipidemia in hypothyroidism may finally lead to cardiovascular diseases [28].

Serum levels of triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol are elevated in full blown hypothyroidism.

In patients with SCH, the same changes are present but are less marked and less consistent. This pattern of lipid abnormalities, of course, is important because it is a risk factor for atherosclerotic cardiovascular disease. Certain studies have shown a decrease in LDL cholesterol and total cholesterol levels after treatment with levothyroxine [29].

The risks and benefits of treating patients with SCH have been debated for two decades. The advantages of treating SCH include, first and most important is preventing the progression to overt hypothyroidism.

Secondly, thyroxine therapy may improve the serum lipid profile and thereby decrease the risk of death from cardiovascular causes. Finally, treatment may reverse the symptoms of mild hypothyroidism, including psychiatric and cognitive abnormalities [30].

### **Cardiovascular effects**

The lipid pattern is particularly altered in SCH patients with a serum TSH greater than 10 mU/l. Vascular dysfunction and dyslipidemia may increase the risk of atherosclerosis in SCH. Endothelial dysfunction at the level of coronary circulation may contribute to the increased risk of CHD in patients with mild SCH[31]. Other cardiac abnormalities detected are prolongation of LV pre-ejection period (PEP) and an increase in ratio between PEP and LV ejection time (LVET) [32]. Abnormalities are seen in both systolic and diastolic functions of the LV in patients with SCH. Decrease in LV ejection fraction (EF) is observed during exercise [33].

In several studies, a sensitive measure of myocardial contractility, the ratio of pre-ejection period to left ventricular ejection time (PEP:LVET) was shown to improve significantly in patients with SCH who were treated with levothyroxine, compared with patients who were treated with placebo[34].

Several studies have indicated that these abnormalities improve with Levothyroxine therapy; thyroid replacement will improve the cardiac output, decrease the systemic vascular resistance, reverse the diastolic dysfunction and importantly improve the left ventricular ejection fraction during exercise [35-38].

SCH was associated with increased risk of myocardial infarction and aortic atherosclerosis in the cross-sectional analysis of the Rotterdam study of at least 55 aged women [39]. Considering all the effects of SCH on cardiovascular system, treatment of this condition with thyroxine will prevent against the development of cardiovascular diseases.

### **Somatic and neuromuscular effects**

Patients with SCH have mild clinical manifestations and non-specific symptoms such as dry skin, cold intolerance, constipation, and easy fatigability [40]. Patients with SHT and muscle symptoms present evidence of mitochondrial oxidative dysfunction. The higher lactate/pyruvate ratio leads to increased lactate level in blood during exercise [41]. According to a study there is also presence of polyneuropathy in SCH patients.

### **Dyslipidemia**

Cholesterol and triglycerides, known as lipids, are fatty substances normally produced by the body. *Dyslipidemia* means lipid levels in the bloodstream are too high or low. The most common types of dyslipidemia are:

High levels of low-density lipoprotein (LDL) cholesterol  
Low levels of high-density lipoprotein (HDL) cholesterol  
High levels of triglycerides [42]

The classification of lipoproteins has traditionally been based on the different density of lipoprotein particles separated by ultracentrifugation. The main classes of lipoproteins are chylomicrons, very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low-density lipoproteins (LDL), lipoprotein(a) [Lp(a)], and high-density lipoproteins (HDL) [43].

### Chylomicrons

Chylomicrons are secreted from the intestine after a fat-containing meal with ApoB-48 as a major protein component. They deliver fat as an energy source for muscles or to adipose tissue for storage. Chylomicrons contain also apoC-I, apoC-II, apoC-III, and apoE. For lipoprotein lipase (LPL) to function properly, they receive more apoC-II from HDL [44].

### VLDL and LDL

The liver uses free fatty acids from the circulation and excess carbohydrates, fat, and proteins from the meal to synthesize triacylglycerides, which form VLDL together with apoB-100, cholesterol and other lipids [45]. The end-point of VLDL-metabolism is LDL, which is the most cholesterol-enriched lipoprotein particle in the blood circulation. LDL is responsible for constant supply of essential cholesterol for tissues and cells. The only protein in LDL particles is apoB-100, which is derived from the VLDL and does not exchange between other lipoproteins during metabolism [46].

### HDL

HDL is secreted from the liver (70 %) or intestine (30%) as lipid-poor nascent particles that contain only ApoA-I and phospholipids. The maturation of HDL from nascent discoidal particle to larger, spherical HDL demands the action of lecithin-cholesterol acyl transferase (LCAT), which converts free cholesterol to cholesterol esters [47].

HDL: bridging past and present with a look at the future. In hypothyroidism the thyroid gland produces minimal amount of thyroid hormone, such patients will lead to have lower metabolic rate and clinical manifestations such as overweight, fatigue, hypotension and depression. The symptoms of thyroid dysfunction can put the patient life at risk, therefore the diagnosis and management of thyroid dysfunctions is an important task for clinicians as well as medical diagnostic laboratories worldwide. Laboratory measurements of TSH, T<sub>4</sub> and T<sub>3</sub> are the key hormones in diagnosing the thyroid abnormality. Generally TSH and T<sub>4</sub> play even a major role in the diagnosis of either hyper or hypothyroidism. Other clinically undiagnosed thyroid abnormalities are either subclinical hyperthyroidism or subclinical hypothyroidism which can be diagnosed on the basis of laboratory blood test results. Whether SCH is associated with any metabolic disorders is not fully understood and it remains unanswered. Thyroid disorder can be correlated with some metabolic abnormalities, such as dyslipidemia, cardiovascular, liver disease and anemia[48].

It is universally accepted that there is an association between dyslipidemia and hypothyroidism patients and since half century ago, there were many studies documented that dyslipidemia in hypothyroidism finally lead to cardiovascular disease [48]. The decreased thyroid function in hypothyroidism is accompanied by reduced activity of HMG-CoA reductase, TC and LDL-C levels are increased in patients with overt hypothyroidism [49].

This is due to the decreased LDL-receptors' activity, resulting in decreased catabolism of LDL and IDL [50]. Moreover, a decrease in LPL activity is found in overt hypothyroidism, decreasing the clearance of TG-rich lipoproteins [51]. Therefore, overt hypothyroid patients may also present with elevated TG levels associated with increased levels of VLDL and occasionally fasting chylomicronemia [52].

Hypothyroid patients may also exhibit increased levels of HDL-C mainly due to increased concentration of HDL<sub>2</sub> particles. Indeed, due to a reduction of HL activity a reduction in HDL<sub>2</sub> catabolism is observed. Moreover, decreased activity of the CETP results in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL-C levels. Hypothyroid patients have elevated Lp (a) levels, which are associated with increased CVD risk. In a study it was documented that HDL metabolism was altered in thyroid dysfunction, and the effect of thyroid hormone on HDL is through its effect on hepatic lipase activity [53].

It is well known that overt hypothyroidism is associated with increased plasma cholesterol, LDL cholesterol and triglyceride levels [54, 58-60]. SCH should be a matter for further investigation because dyslipidemia is associated with this thyroid disorder. But the relationship between SCH and dyslipidemia is still controversial about whether SCH is constantly and universally associated with lipid disorder. Few large cross sectional studies reported that there were no significant differences among total cholesterol or LDL cholesterol between subjects with SCH and healthy adults. But some cross sectional studies reported elevation of total cholesterol and LDL cholesterol among subclinical hypothyroid compared to healthy subjects [48]. There are also studies, that reported even total cholesterol of female patients with SCH was even lower than euthyroid women [55] but this type of report is very rare and cannot be taken seriously. Already the author of review article [48] reported that the lipid profile in women with subclinical hypothyroid, compared to euthyroid females are elevated [56].

Some studies documented that SCH is associated not only with LDL-cholesterol levels and HDL-cholesterol levels but also with elevated Lp (a) [57]. In another study in this respect, it was detected that subjects with SCH also had significantly higher levels of Apo A and ApoB with elevated LDL cholesterol and total cholesterol [61].

Thyroid hormone has multiple effects on the regulation of lipid synthesis, absorption, and metabolism. Studies consistently demonstrate increased levels of serum TC, LDL-C, ApoB, Lp (a), and possibly triglycerides in individuals with overt hypothyroidism, all of which are reversible with levothyroxine therapy. Although it is found that 1 to 11% of all patients with dyslipidemia have SCH, the effects of SCH on serum lipid values are not that much clear. ApoB levels may be increased in patients with SCH. Although some studies have demonstrated that total cholesterol and LDL-C levels are raised in patients with SCH, others have not shown any effect of SCH on these lipid measurements. Serum triglycerides, lipid sub particle size, and LDL-C oxidizability may be altered in SCH, but these studies have also been inconsistent. The evidence suggests that HDL-C and lipoprotein (a) levels are not altered in sub clinically hypothyroid patients. Smoking and insulin resistance may modify the effects of SCH on serum lipid values. Clinical trials up to date have not consistently shown a beneficial effect of levothyroxine treatment on serum lipid levels in sub clinically hypothyroid patients [62].

The nature and degree of dyslipidemia in overt hypothyroidism has been demonstrated in many studies and there is no doubt about the beneficial effects of thyroid substitution on serum lipids and on the risk for CAD. However, the possible effects of small alterations of thyroid function on lipid profile and atherogenesis is less clear. There is, in fact, doubt as to whether SCH should be treated [63]. The evidence provided by different author's concerns different aspects of this condition and it is controversial. There is growing evidence, that SCH is a risk factor atherosclerosis and myocardial infarction in elderly women [39]. In substantial number of studies TC and LDL-C seem to be elevated in SCH compared with control [64].

However some studies do not confirm this observation. In this respect, in our cohort, subjects with SCH had significantly higher levels of TC, LDL-C, Apo B and Lp(a), thus displaying a more atherogenic lipid profile when compared with healthy individuals. The lipid response to L-thyroxine substitution is another, yet clinically very important matter. The results of previous studies have been inconsistent [63].

Cardiovascular system is very sensitive to minimal defects of circulating thyroid hormone and cardiovascular diseases are associated with overt hypothyroidism. The abnormalities in myocardial contractility and the changes of lipoprotein profile are frequently documented in hypo-thyroid patients. Therefore SCH may be considered a true risk factor for the development of coronary heart disease. 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. With advancing age subjects that are relatively resistant to the adverse vascular effect of SCH may survive, leading to an attenuation of this effect in old age [65].

In a case control study done in India TC, LDL-C, HDL-C, VLDL-C and triglyceride from 100 patients in the age range of 15-65 years of both sex having SCH were compared with euthyroid controls to find out whether SCH is associated with abnormal lipid levels or not in a population-based sample. A considerable increase in triglycerides and VLDL-C levels were observed in patients of SCH with respect to euthyroid controls while a nominal increase in serum cholesterol, LDL-C and HDL-C were detected. However, there was no statistical difference found in any of the lipid fraction levels with change in the severity of SCH. All these observation suggested that SCH did not have a marked impact on any of the fraction of lipids [66].

Whickham survey defined that younger women with a mildly TSH level (6-9mU/L) had a lower risk for progression. The risk of progression was unevenly distributed throughout the follow up period. In patients with SCH and increased total cholesterol level, levothyroxine treatment may reduce serum cholesterol and thereby decrease the incidence of CAD, Stroke, and Peripheral Vascular disease [69].

## **TREATMENT**

Indications for treatment in SCH are not well established, but general guidelines can be offered. Greater magnitude and duration of TSH elevation and higher titres of antithyroid antibodies increase the probability that the condition will progress to overt hypothyroidism and, therefore, increase the potential benefit of treatment with levothyroxine. The presence of symptoms related to mild hypothyroidism also increases the potential benefit of treatment. Risk of harm to the patient, against which this potential benefit must be balanced, is quite minimal, since the use of the sensitive TSH assay provides assurance that we are not raising the blood thyroid hormone levels too much as long as TSH levels do not fall below the normal range. In patients with CAD and minimal elevations of TSH, however, it may be advisable to follow the TSH level rather than subject the patient to the small risk of levothyroxine therapy [67].

Patients with SCH, because of the minimal extent of the thyroid hormone deficiency, may be treated with total daily dosages of levothyroxine as low as 25 to 50 µg. This initial dosage should be maintained for six to eight weeks before a TSH measurement is repeated to guide adjustment of the levothyroxine dosage. The goal is to maintain the TSH



level within normal limits; the dosage of levothyroxine should be increased if the TSH level remains above normal and should be decreased if the TSH level falls below normal. Once the correct dosage of thyroxine is established, the frequency of TSH measurement may be decreased to every six to 12 months [67].

### **Screening**

Screening for thyroid dysfunction can be performed using the medical history, physical examination, or any of several serum thyroid function tests. The TSH is usually recommended because it can detect abnormalities before other tests become abnormal. When used to confirm suspected disease in patients referred to an endocrine specialty clinic, the TSH test has sensitivity above 98% and specificity greater than 92% for the clinical and functional diagnosis. The accuracy of TSH screening in primary care patients is difficult to evaluate, as TSH is often considered the “gold standard” for assessing thyroid function [68]. American College of Physicians recommends screening women older than age 50 with one or more general symptoms that could be caused by thyroid disease. The American Association of Clinical Endocrinologists recommends TSH measurement in women of childbearing age before pregnancy or during the first trimester. The American Thyroid Association recommends measuring thyroid function in all adults beginning at age 35 years and every 5 years thereafter, noting that more frequent screening may be appropriate in high-risk or symptomatic individuals [68].

A potential benefit of treating SCH is to prevent the spontaneous development of overt hypothyroidism [68].

### **MATERIALS AND METHODS**

This study was conducted at department of biochemistry, Karuna Medical College and Hospital, Vilayodi, Chittur, Kerala a teaching hospital attached to Kerala University of Health Sciences, Thrissur, Kerala.

Study design: Descriptive case control study.

Study period and duration: The present case control study was conducted during the period of October 2012 to October 2013.

### **Source of data**

Serum samples with TSH values falling within the subclinical hypothyroidism range and having euthyroid status were identified at the central biochemistry laboratory and their particulars were matched according to the inclusion criteria. The serum samples were collected from patients attending the medicine and gynaecology OPD of Karuna Medical College and Hospital, Vilayodi, Kerala.

### **Sampling procedure**

Total sample size selected for the study was 50 of which 25 were of subclinical hypothyroidism and 25 were euthyroid controls. Fasting blood samples of about 5 ml were collected taking aseptic precautions in a red capped vacutainer. Blood samples were then centrifuged at 3000 rpm for 10 minutes and the serum was separated for further tests.

### **Inclusion criteria**

Patients above 18 years and up to 65 years of age with elevated TSH levels (4.2-20  $\mu$ IU/mL) [73] and normal T3 and T4 levels. Patients with newly diagnosed and untreated cases for sub clinical hypothyroidism.

### **Exclusion criteria**

Patients suffering from diabetes, polycystic ovarian disease, Tuberculosis, other systemic illness, liver disorders, renal disorders, congestive cardiac failure, intake of oral contraceptive pills, statins and other medications that alter thyroid functions and lipid levels led to exclusion from the study. Pregnancy also accounted for exclusion from the study.

### **Ethical clearance**

Before the commencement of the study Ethical clearance was obtained from the Ethical Committee of Karuna Medical College and Hospital, Vilayodi, Kerala.

### **Informed consent**

All the patients fulfilling selection criteria were explained about the purpose of the study and a written informed consent was obtained before enrolment. (Annexure I).

### **Test done**

### **T3, T4, TSH: by chemiluminescence immunoassay (acculite)**

Immobilization takes place during the assay at the surface of an opaque chemiluminescent reaction cell through the interaction of streptavidin coated on the opaque reaction cell and exogenously added biotinylated monoclonal antibody coupled to the analyte of interest. Reaction results between the native antigen and the antibodies. The enzyme activity, determined by reaction with a substrate that generates light, in the antibody-bound fraction is directly proportional to the native antigen concentration.

#### SENSITIVITY

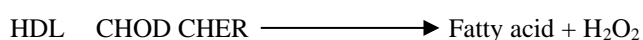
TSH: 0.03 $\mu$  IU /ml

T3: 0.04ng/ml

T4: 0.01 $\mu$ g/ml

#### HDL by direct method (liquid stable reagent) (erba Mannheim EM 200)

The assay is based on a modified polyvinyl sulfonic acid (PVS) and polyethylene-glycol-methyl ether coupled classic precipitation method. The enzymes selectively react with HDL to produce H<sub>2</sub>O<sub>2</sub> which is detected through a trinder reaction.



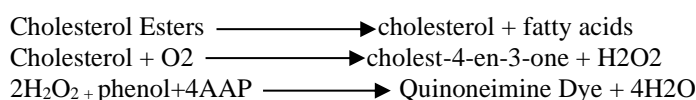
#### SENSITIVITY

HDL: 1.06mg/dl

#### Serum Cholesterol By Cholesterol Esterase, Cholesterol Oxidase Peroxidase Method

CHOLESTEROL esters are enzymatically hydrolysed by cholesterol esterase to cholesterol and free fatty acids.

Free cholesterol, including that originally present, is then oxidized by cholesterol oxidase to cholest-4-en-3-one and hydrogen peroxide. It combines with 4-aminoantipyrine to form a chromophore which may be quantiated at 505nm.

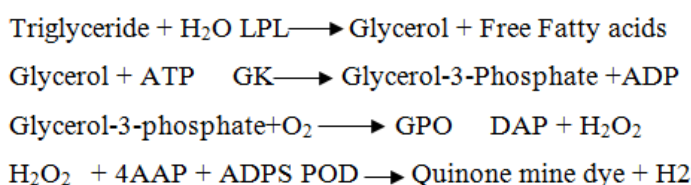


#### SENSITIVITY

Total Cholesterol: 1mg/dl

#### Triglyceride by GPO\_ADPS method

Triglyceride is enzymatically hydrolyzed by lipase to free fatty acids and glycerol. Then the glycerol is phosphorylated by adenosine triphosphate with glycerol kinase to produced glycerol 3 phosphates and adenosine diphosphate. Glycerol 3 phosphates are oxidized to dihydroxy acetone phosphate producing hydrogen peroxide. The hydrogen peroxide reacts with 4 amino antipyrine and 4 chlorophenol to produce red coloured dye. The absorbance of the dye is proportional to the concentration of triglyceride present in the sample.



#### SENSITIVITY

Triglycerides: 2mg/dl

VLDL may be calculated using the Friedewald's equation:

VLDL = Triglycerides/5

LDL = cholesterol - (HDL + VLDL)

#### NORMAL VALUES as per (NCEP) ATP III MAY 2001

CHOLESTEROL = <200 mg/dl

LDL = <130 mg/dl

HDL = >59 mg/dl  
 VLDL = <30mg/dl  
 TRIGLYCERIDES = <150mg/dl

**RESULTS**

The present case control study was conducted in 50 patients aged from 18 to 65 years (25 subclinical hypothyroidism cases and 25 euthyroid controls). Among the cases majority (40%) were in the age group of 30-45 years (Table 3, Figure 4). The thyroid profile was assessed by estimating TSH, T<sub>3</sub> and T<sub>4</sub> and fasting lipid profile was done in both cases and controls. Data was analysed using SPSS16 SOFTWARE .To analyze and compare the groups, both descriptive and inferential statistics were used. The continuous data was assessed for the normality and accordingly appropriate parametric test were used. To compare the variables which follow normal distribution? The comparison between the groups was done using independent samples test and Pearsons correlation test.

With respect to the age, mean age of cases and controls were 40.68 and 33.57 years respectively the sample study consisted of 88 % of females and 12% males in the subclinical hypothyroidism population and 76% females and 24% males in control group (Table 3, Graph 1) The mean T<sub>3</sub> among Sub Clinical Hypothyroidism was 1.03± 0.34 and in controls was 0.90 ±0.24 (p 0.121) mean T<sub>4</sub> among Sub Clinical Hypothyroidism was 7.7 ±1.33 and in controls was 8.7 ± 1.77 (p = 0.024) The mean TSH was Sub Clinical Hypothyroidism was 10.7± 1.33 and in controls was 2.95±3.60.

The mean Cholesterol levels were 276.1±73.56 and 178.48±52.24 in Sub Clinical Hypothyroidism and control groups respectively. Among males mean cholesterol levels were 244.3± 38.9 and 178.5 ± 25.9, in subclinical hypothyroidism and control groups respectively. Among females mean cholesterol levels were 277.7± 68.0 and 150.3±29.1 in sub clinical hypothyroidism and control groups respectively, which showed mean cholesterol levels of females was more than males in sub clinical hypothyroid groups. (p – Value <0.05). (Figure 4,5)

The mean triglyceride levels were 156.64±45.38 and 110.68±41.37 in sub clinical hypothyroidism and control groups respectively. Which shows that triglycerides level is increased in subclinical hypothyroid cases than controls. The mean HDL-cholesterol levels were 50.88 ±13.62 and 54.52±14.06 in sub clinical hypothyroidism and control groups respectively, which showed mean HDL – cholesterol levels was lower in sub clinical hypothyroid groups but not that much significant. The mean LDL-cholesterol levels were 191.7 ±72.51 and 80.4±24.28 in sub clinical hypothyroidism and control groups respectively. Which showed mean LDL – cholesterol levels was more in sub clinical hypothyroid groups compared to the controls. (p – Value <0.05) (Graph 3, table 6).

The Pearson’s correlation coefficient for the relationships between serum TSH and lipid parameters are shown in (Table 5).Our study showed that TSH levels were positively correlated with cholesterol, LDL and negatively with HDL in patients with Subclinical hypothyroidism (r=0.685, P<0.01; r=0.947,P<0.01;r= -.553,P=<0.01 respectively). The serum TSH levels have no significant correlation with triglycerides and VLDL levels.

According to the analysis there is a significant increase in mean cholesterol, mean LDL values, and a minimal increase in mean triglyceride values in cases compared to controls. There is no significant variation in HDL and VLDL levels (Fig 3).

**Table-3: Sex distribution among cases & controls**

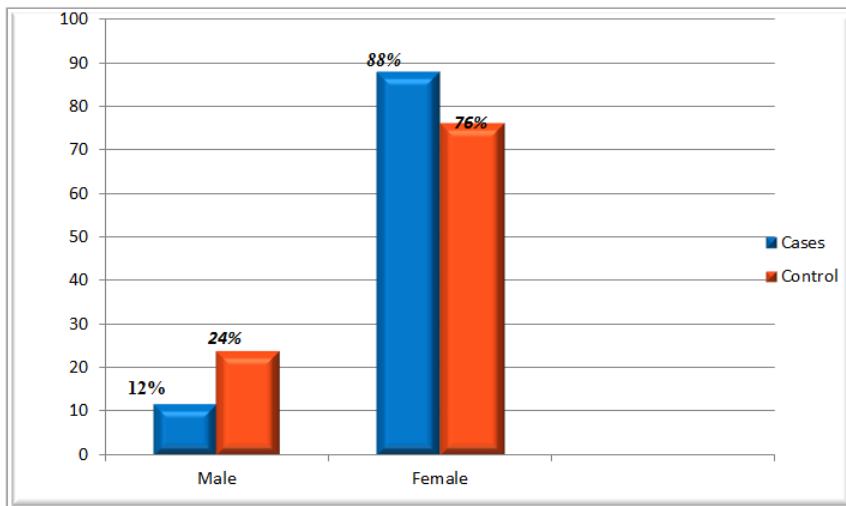
Sex	Cases (N=25)		Controls (N=25)	
	Number	Percent	Number	Percent
Male	3	12	6	24
Female	22	88	19	76

$\chi^2 = 1.22; P = 0.135$

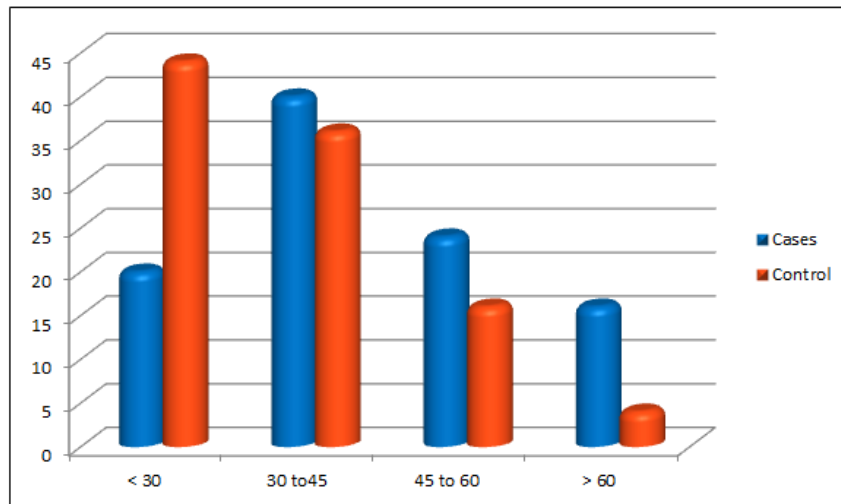
**Table-4: Age distribution among cases & controls**

Age Group (yrs)	Cases (N=25)		Controls (N=25)	
	Number	Percent	Number	Percent
<30	5	20	11	44
30 to 45	10	40	9	36
45 to 60	6	24	4	16
> 60	4	16	1	4

$\chi^2 = 4.503$   
 P value = 0.212



Graph-1: Bar graph showing Sex distribution among cases and controls



Graph-2: Bar graph showing Age distribution among cases and control

Table-5: Correlation between tsh and lipid parameters

Parameter	Correlation Coefficient(r)	P Value
TSH vs. Cholesterol	0.685	P=<0.01*
TSH VS LDL	0.947	P=<0.01*
TSH VS HDL	-0.553	P=<0.01*
TSH VS Triglycerides	0.265	P=0.2
TSH VS VLDL	0.241	P=0.2

\* Statistically significant

Table-6: Analysis of parameters in cases (subclinical hypothyroid) and controls

Parameter	Subclinical hypothyroid(cases)	Controls	Comparison
TSH	10.77 ± 3.79	2.95± 3.60	T=7.074 p=.000
T3	1.03 ± 0.34	0.90 ± 0.24	T=1.580 p=0.121
T4	7.70 ± 1.33	8.74± 1.77	T=2.330 p=.024
HDL	50.88± 13.62	54.52± 14.06	T=-.929 p=.357
LDL	191.78± 72.51	80.42± 24.28	T=7.281p=.000
VLDL	31.13± 9.13	22.13± 8.27	T=3.651p=.001
Cholesterol	276.10± 73.56	178.48± 52.24	T=5.201 p=.000
Triglycerides	154.64± 45.38	110.68± 41.37	T=3.579 p=.001

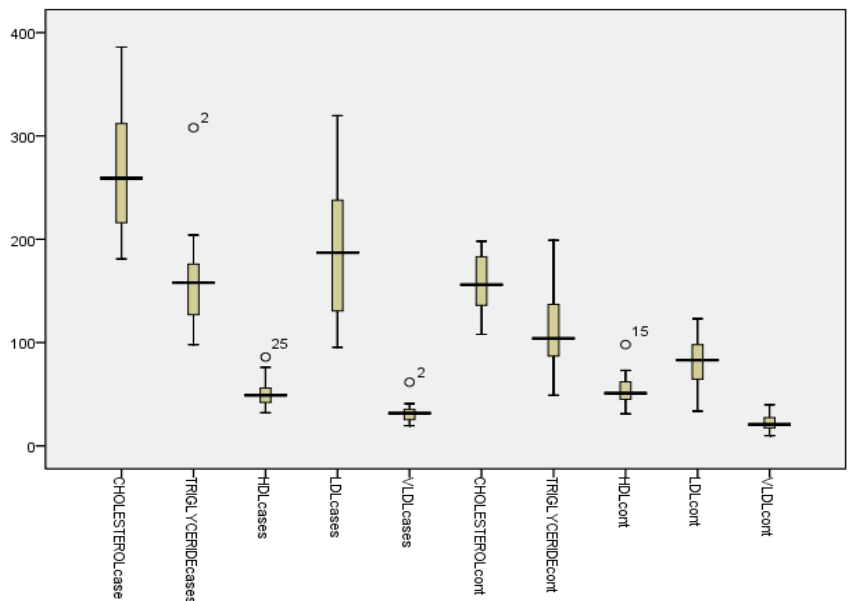


Fig-3: Box plots showing variation of lipid profile in cases and controls

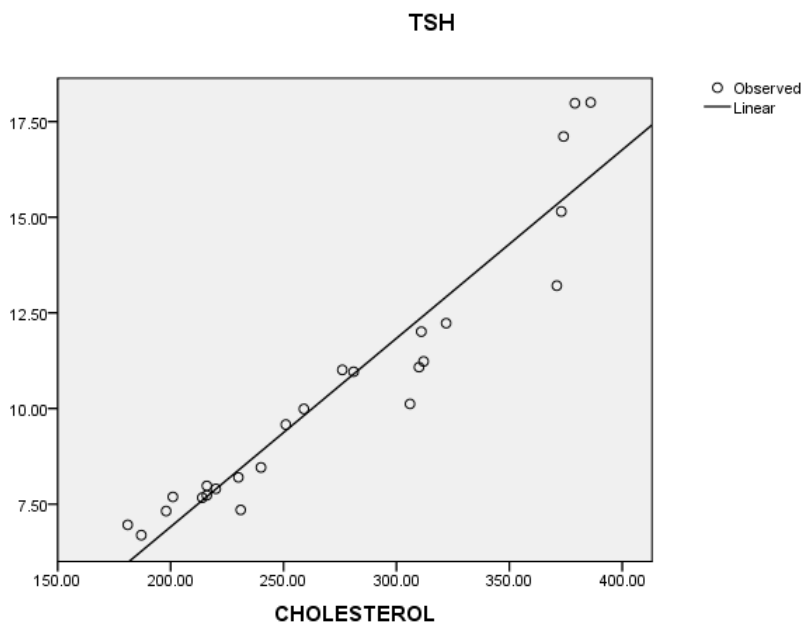
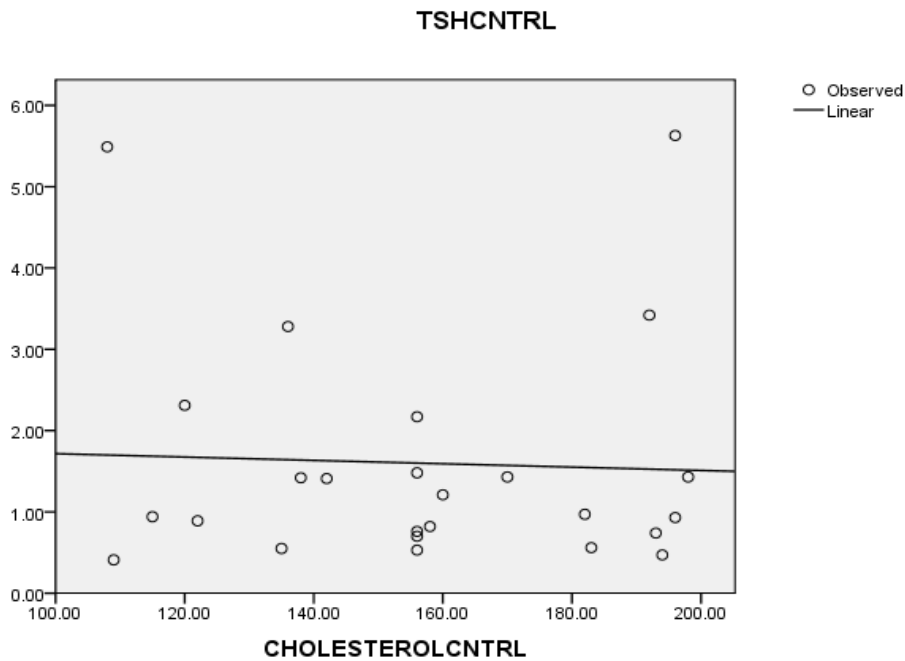
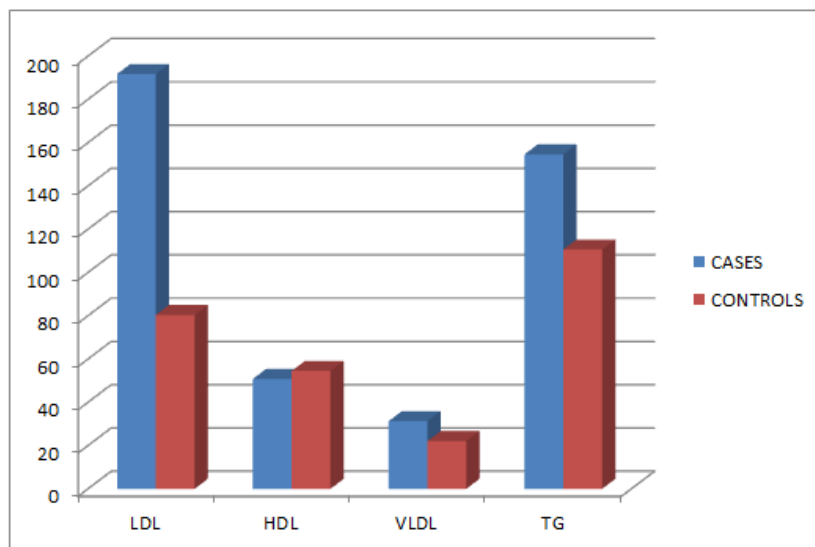


Fig-4: Linear regression curve showing correlation between subclinical hypothyroid cases and cholesterol level



**Fig-5:** linear regression showing correlation between CONTROLS and cholesterol



**Graph-3:** Mean values of LDL, HDL, VLDL and Triglycerides in CASES and CONTROLS

## DISCUSSION

Thyroid disorders are one of the most common endocrinal disorders worldwide. The symptoms of subclinical hypothyroidism are vague and non-specific. It is diagnosed by normal thyroxine ( $T_4$ ) and normal tri iodothyronine ( $T_3$ ) and an elevated TSH level.

SCH is an independent risk factor for aortic atherosclerosis and myocardial infarction. However, the results of lipid profile alterations in subclinical hypothyroidism are controversial in different studies; some have showed that there is positive correlation[76] and prompt reversal of changes following treatment [66], while others have not shown any correlation between the two[66]. Further, there are very few Indian studies on association between SCH and dyslipidemia. The present study was aimed to determine the association between SCH and dyslipidemia.

This study was conducted at department of biochemistry, Karuna Medical College and Hospital, Vilayodi, Chittur, Kerala a teaching hospital attached to Kerala University of Health Sciences, Thrissur, Kerala. The present case control study was conducted during the period of October 2012 to October 2013.

A total of 50 patients (25 cases and 25 euthyroid controls) were studied. In the present study, among cases, 88% were females when compared to 76% in controls ( $p=0.135$ ). This study showed female predominance which was similar to study done at Calcutta, where females constituted 78% of study populations. Some studies done in Punjab [66] and New Delhi where females was 88% & 80.22% of the study population respectively.

The mean age of cases and controls were 40.68 and 33.57 years respectively which was similar to a study done at Calcutta<sup>74</sup> where it was 38.56 years and  $31.55 \pm 2.1$  years in another study done in New Delhi and in controls mean age was 20.46 years ( $p<0.001$ ).

In this study all the cases had mildly elevated TSH levels (5-19  $\mu\text{IU/ml}$ ) and normal T3 and T4 levels as defined by inclusion criteria which are similar to a study done in Punjab [66] and New Delhi [75] where the cut off limit for TSH was  $> 5.0 \mu\text{IU/ml}$  and  $6.1 \mu\text{IU/ml}$  respectively. In the present study, it was observed that mean TSH level was significantly high in cases compared to controls ( $10.77 + 3.79$  vs  $2.95 + 3.60 \mu\text{IU/mL}$ ;  $p<0.001$ ). This finding was similar to a study done in New Delhi<sup>75</sup> where mean TSH was  $7.615 \pm 0.11 \mu\text{IU/mL}$ .

In the present study, we observed that the mean values of cases had high Cholesterol ( $>200 \text{ mg/dl}$ ), LDL values ( $>130 \text{ mg/dl}$ ) compared to controls. However this difference was statistically significant ( $p< 0.01$ ). These findings are similar to a study done in Uttar Pradesh where there was a statistical difference seen between cholesterol, LDL and TSH levels.

Hypertriglyceridemia is a well-known risk factor for cardiovascular diseases like atherosclerosis. 80% of the cases had high triglycerides ( $>150 \text{ mg/dL}$ ) compared to controls. This difference was statistically significant ( $p<0.01$ ). These findings are similar to a study done in Punjab [66] where mean triglycerides levels were  $174.78 \pm 32.92 \text{ mg/dL}$ .

No significant difference was noted when T3 and T4 levels were compared among cases and controls. T3 levels between cases and controls were similar. This is an expected finding because peripheral deiodination of T4 to T3 is not affected in subclinical hypothyroidism. Hypothyroidism results in a rise in circulating total cholesterol and LDL cholesterol levels.

The changes in plasma lipids in hypothyroidism result in an atherogenic lipid profile. Cardiovascular system is very sensitive to mild defects of circulating thyroid hormone and cardiovascular diseases are associated with overt hypothyroidism. The abnormalities in myocardial contractility and the changes of lipoprotein profile are frequently found in hypo-thyroid patients. Therefore SCH may be considered a true risk factor for the development of coronary heart disease [78]. At a younger age, SCH has severe pathophysiological effects resulting in increased vascular disease through dyslipidemia, endothelial dysfunction or a direct effect on myocardium. With advancing age subjects that are relatively resistant to the vascular effect of SCH may survive, leading to an attenuation of this effect in old age.

Whickham survey defined that younger women with a mildly TSH level (6-9mU/L) had a lower risk for progression. The risk of progression was unevenly distributed throughout the follow up period. In patients with SCH and with increased total cholesterol level, L-thyroxine treatment may reduce serum cholesterol and thereby decrease the incidence of coronary artery disease, stroke, and peripheral vascular disease.

## **CONCLUSION**

The present study showed significantly higher levels of cholesterol, triglycerides and low density lipoprotein levels were associated with sub-clinical hypothyroidism. The Quantitative analysis showed significantly raised serum cholesterol levels among Patients with subclinical hypothyroidism. Statistically significant relation was also found between, low density lipoprotein and triglycerides and subclinical hypothyroidism. Majority of the SCH subjects had dyslipidemia and TSH levels were significantly correlated with total cholesterol, LDL cholesterol and triglycerides.

It seems necessary that subjects with laboratory report of Hypercholesterolemia and hypertriglyceridemia should be also further examined and tested for underlying hypothyroidism. The evaluation of thyroid stimulating hormone (TSH) should be reassessed carefully as it provides the information on the thyroid status. Larger studies are required to clarify the significance of development of Dyslipidemias in subclinical hypothyroid subjects before the development of overt hypothyroidism. The lipid levels and serum TSH should be considered under routine screening. Latest parameters of thyroid function like anti-TPO, Anti Tg antibodies will probably help predict the occurrences of hypothyroidism. Lipid

parameters like atherogenic index, apoA, apoB100, apoA: apoB100 needs to be evaluated to uncover the underlying pathogenesis.

## SUMMARY

Subclinical hypothyroidism may be associated with increased risk of CAD, PVD and various biochemical abnormalities including increased LDL-C Levels, increased total cholesterol and serum triglyceride values. It is uncertain whether subclinical hypothyroidism (increased serum TSH, normal serum T4 and T3) is also associated with dyslipidemia. The present study was aimed to determine lipid abnormalities in patients with subclinical hypothyroidism and its interpretation.

This study was conducted at department of biochemistry, Karuna Medical College and Hospital, Vilayodi, Chittur, Kerala a teaching hospital attached to Kerala University of Health Sciences, Thrissur, Kerala. From October 2012 – October 2013.

A total of 50 patients (25 cases with subclinical Hypothyroidism and 25 euthyroid controls) were studied. The thyroid profile was assessed by estimating TSH, T3 and T4. Using a semi-automated chemiluminescence immunoenzymometric assay.

Among the cases, 88% had high cholesterol, 68% had high triglycerides and 72% had high LDL, the present study showed significantly higher levels of cholesterol, triglycerides and low density lipoprotein levels in patients with sub-clinical hypothyroidism.

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