ASSOCIATION OF THYROID FUNCTION ABNORMALATIES AND SERUM LIPIDS - A REVIEW ARTICLE

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ABSTRACT

Thyroid disease such as hypothyroidism and hyperthyroidism are the most prevalent hormonal disorders in these years. The thyroid disease can be diagnosed in the form of clinical and subclinical form. Thyroid disease is described as "The alteration in serum thyroid stimulating hormone level with normal or altered thyroid hormones". Thyroid hormones involve in the synthesis, mobilization and degradation of lipids. The degradation effects of thyroid hormones are more predominant than the synthesis effects in lipids. The association between thyroid disorders and lipids has been known for 70 years ago in the term of hypercholesterolemia. Because the thyroid hormones involve in the regulation of some key enzymes activity in lipids transport. Hydroxy methyl glutaryl coenzyme redcutase involve in the synthesis of cholesterol. Presence of free intracellular cholesterol inhibits HMG CoA reducatase thus; the cholesterol synthesis decreases. But the thyroid hormones induce the HMG-CoA reductase and the enzyme directly increases the synthesis of cholesterol. Many observational studies approved that the level of Total cholesterol, Triglycerides, very low-density lipoprotein and low density lipoprotein increase above the normal range and the high density lipoprotein decrease from the normal range in overt hypothyroidism. Thyroid stimulating hormones have deleterious effect on serum lipids thus; elevation in TSH values directly might change lipids values. The studies suggested that the TSH has adipogenesis and lipolysis effects. As well as, TSH increase the activity of HMG-CoA reductase thus; increase the cholesterol level in hepatocytes. The studies suggested that the prevalence of hyperthyroidism is decreased in hyperlipidemic patients. In a study reported that the prevalence of hyperthyroidism is 3 out of 248 hyperlipidemic patients.

KEYWORDS: Thyroid stimulating hormone, Thyroid hormones, Thyroid dysfunctions, Serum Lipids

INTRODUCTION

It was clear that the compositions and values of plasma lipids will change in overt and subclinical hypothyroidism and overt and subclinical hyperthyroidism. Because the thyroid hormones involve in the regulation of some key enzymes activity in lipids transport. Hydroxy methyl glutaryl coenzyme A (HMG CoA) redcutase involve in the synthesis of cholesterol. Presence of free intracellular cholesterol inhibit HMG CoA reducatase enzyme thus, the cholesterol synthesis decrease. But the thyroid hormones induce the HMG-CoA reductase than this enzyme directly increases the synthesis of cholesterol. It means that the level of cholesterol increases in hyperthyroidism and decreases in hypothyroidism. In contrast the level of serum cholesterol not only affected by cholesterol synthesis but also affected by cholesterol degradation. It means

that the level of cholesterol decreases in hyperthyroidism and increase in hypothyroidism because of cholesterol synthesis and degradation being affected by thyroid hormones at the same time [1 - 4].

One of the reasons which suggest the lowering effect of cholesterol by thyroid hormones is increasing in the expression of the Low Density Lipoprotein (LDL) receptors at the hepatic and peripheral tissues. Tri Iodo Thyronin (T3) regulates the LDL receptors which decrease the elimination of LDL cholesterol and regulate the number of LDL receptors in humans. It was suggested that the level of LDL receptors mRNA were decreased in the hepatocyte of rats [2-4]. A study suggested that the 3 % of the tetraiodo thyronin (T4) is bind to High Density Lipoprotein (HDL) (92%) and LDL (6.7%). LDL receptors recognized the T4-LDL complex and finally T4 enters to the cells and increases the catabolic rate of apoB [2-3]. T3 bind to the thyroid hormone responsive elements (TREs). T3 regulate the LDL receptor gene by controlling the sterol regulatory element-binding protein-2 (SREBP-2) and prevent LDL oxidation [4].

HDL concentration may be normal or increased in severe hypothyroidism and normal or decreased in hyperthyroidism [1-2, 4-6]. Because the thyroid hormone increases the activity of cholesterol ester transfer protein (CETP) thus, CETP transfer the cholesterol ester from the HDL2 to the Very Low Density Lipoprotein (VLDL), Intermediate Density Lipoprotein (IDL) and chylomicron and triglyceride (TG) to the HDL2 [1, 4]. Also reported that the activity of hepatic lipase (HL) increases by thyroid hormones thus, HL convert HDL2 to HDL3. It means that the activity of CETP and HL increases in hyperthyroidism and inversely decreases in hypothyroidism. The conversion of the HDL2 to HDL3 and IDL to LDL is happening because of HL activity [1-2, 4].

THYROID GLAND DISORDERS

Thyroid disorders has been known since thousands years. Goiter is one of the thyroid gland dysfunction which was known by Chinese people in 1600 BC [7]. Thyroid diseases are the condition which the normal function of thyroid glands has impaired with many factors [8]. Thyroid gland disorders may be caused through excess synthesis (hyperthyroidism or thyrotoxicosis) and less synthesis (hypothyroidism) of both the thyroid hormones. In the thyroid disorders the clinical manifestation may be ranging from subclinical disorders up to life threating conditions. The mild form of dysfunction is mostly the common form of thyroid dysfunction. Thyroid disorders start in a slow process without any specific signs and symptoms and develop over times (months and years) which are diagnosed by coming signs and symptoms [9]. Thyroid disorders are the most prevalent hormonal disorders in the world. These disorders are the most prevalent endocrine disorders in the India too. The different studies reported that the prevalence of thyroid disorders is about 42 million people in India [10].

(a) Hypothyroidism

Hypothyroidism is the condition which thyroid gland doesn't produce normal amount of thyroid hormones in the targets tissues [11-12]. Hypothyroidism is mostly common in female, older age groups and certain ethnic groups (white individuals). Hypothyroidism can be overt/clinical primary hypothyroidism and mild or subclinical hypothyroidism. Clinical/overt hypothyroidism is the condition which the levels of thyroid stimulating hormone (TSH) increased and level of FT4 decreased but in mild or subclinical hypothyroidism (SCH) the levels of FT4 remain in normal and TSH getting increased [13-15]. The prevalence of hypothyroidism in UK is about 1-2% [16]. In another study in Colombia showed that the prevalence of hypothyroidism is 2-8%. This study reported that the prevalence of hypothyroidism increase with age, gender (female) and socio-economic status. Pedro Vargas Navarro et al (2010) in 105 patients with psychiatric disorders in Montserrat Hospital at Colombia after a cross sectional study reported that the prevalence of hypothyroidism is 10.5% [15]. There is another study which reported that the prevalence of overt hypothyroidism is 0.3%-3.7% in USA and 0.2%-5.3% in Europe. In a different study the prevalence of overt hypothyroidism is 0.3% and in SCH 4.3% in USA [13-14]. The risk factors for hypothyroidism are some autoimmune diseases such as autoimmune gastric atrophy, diabetes mellitus type 1, coeliac disease and Down's syndrome. But some factors such as smoking and moderate alcohol uptake decreases the level of hypothyroidism [14].

Hypothyroidism can be caused by thyroid hormones deficiency (primary hypothyroidism), TSH deficiency (secondary hypothyroidism), and thyrotrophic releasing hormone deficiency (tertiary hypothyroidism and extra-thyroidal (peripheral hypothyroidism). Secondary, tertiary and peripheral hypothyroidisms are rare (less than 1%) in general population [13-14]. The most important causes of primary hypothyroidism are autoimmune diseases such as Hashimoto's thyroiditis and atrophic autoimmune thyroiditis. But there are some other factors which causes primary hypothyroidism such as previous hyperthyroidism treatment with surgery or radioactive iodine, iodine deficiency, drugs (anti-thyroid drugs, lithium, Amiodarone, interferon-α) and destructive thyroiditis. The causes of secondary hypothyroidism are pituitary or hypothalamic disease [16-17]. The clinical manifestation for hypothyroidism are lethargy, weight gain, cold intolerance, goiter, bradycardia, cardiac failure, angina, muscle aches, constipation, hoarse voice, myalgia, depression, psychosis, anemia, dry skin, myxedema ,alopecia, vitiligo, menorrhagia, infertility, growth retardation, mental retardation, delayed puberty, and hyperlipidemia [13, 15-16, 18].

There are some biochemical tests for diagnosis of hypothyroidism. Increased serum level of TSH and decreased in (Free T4) FT4 suggest primary hypothyroidism. In overt hypothyroidism the serum level of TSH increased but the level of FT3 and FT4 getting decreased. In secondary hypothyroidism suggested decrease level of FT4 and maintain serum TSH level between the reference ranges. In secondary

hypothyroidism more tests also necessary. In Hashimoto's thyroiditis the presence of antithyroid antibodies and thyroid peroxidase are also positive [16].

(b) Subclinical hypothyroidism

Subclinical hypothyroidism (SCH) is defined by increase serum TSH and normal thyroid hormones. TSH elevation is too much sensitive to describe the thyroid gland dysfunctions [16-17, 19]. SCH indicate the primary stage of thyroid dysfunction [14]. Thyroid hormones have indirect relation with TSH level [16]. The prevalence of SCH is about 5-10% of the general population and more common in women with elder age groups than men. Another study support the prevalence of SCH is 4-20% of population. SCH is varies according to race, dietary iodine intake, age, gender and body mass index [17]. The most prevalent causes of SCH is autoimmune thyroiditis [16, 18].

High serum level thyroid antibodies treat with radio iodine or surgery and high iodine intake lead to SCH progress to overt hypothyroidism [16-17]. It means that SCH can be progressive or reversible. SCH can be diagnosed by personal and family history, pharmacological information and clinical evaluation. A high thyroid antibodies concentration is associated with high level of TSH concentration. Some factors such as race, age, body mass index, over weight and obesity are involved in TSH alteration. If SCH patients not treated after a long time, it will induce cardiovascular and metabolic changes. It is all because of decreased expression of sarcoplasmic reticulum calcium ATPase and function of systolic and diastolic. Long term untreated SCH may lead to hypertension, cardiovascular abnormalities, endothelial dysfunctions, increased arterial stiffness and dyslipidemia. Thus, these factors increase cardiovascular mortality and morbidity by coronary heart disease, heart failure and atherosclerosis [17].

(c) Hyperthyroidism

Hyperthyroidism is the condition where the thyroid gland produces, secrete and release excess amount of thyroid hormones [20-21]. The inappropriate amount of thyroid hormones in serum leads to different metabolic abnormalities. Thyrotoxicosis is the condition which occurs due to excess amount of thyroid hormones of any causes such as exogenous intake or release of stored thyroid hormones. Thyroiditis is the inflammations form of thyroid gland which resulting excessive releasing of stored thyroid hormones. Thyroiditis is a common cause of thyrotoxicosis. The clinical manifestation of hyperthyroidism is different from subclinical hyperthyroidism (symptomless) to thyroid storm (potentially fatal), which the thyroid storm is an emergency condition [21].

In Iodine sufficient areas, the most prevalent causes of hyperthyroidism are Grave's disease [22-23]. The factors such as immunotolerance, increasing level of autoantibodies, genetic factors, psychological stress, smoking and female sex are the risk factors for grave's diseases. The genes which are important in causes of graves diseases are immune-regulatory genes, thyroglobulin genes and TSH-receptor genes [24]. Other

factors such as microbes (*Yersinia enterocolitica*), vitamin D deficiency, psychological stress, smoking, females, selenium deficiency, mechanical damage to thyroid and some drugs are potential risk factors for causes of grave's diseases [24-28].

Another study suggested that toxic adenoma and multinodular goiter are the other causes for hyperthyroidism [29]. Thyrotropin-induced thyrotoxicosis and trophoblastic tumor are not significant causes of hyperthyroidism. The causes of thyrotoxicosis without hyperthyroidism are silent thyroiditis, post-partum thyroiditis, and sub-acute painful thyroiditis. These factors destroy the thyroid gland cells which lead to release preformed thyroid hormones to circulation. But the causes of thyrotoxicosis without hyperthyroidism are not more common and it is only for a short period of time [20, 30].

The excess amount of thyroid hormones affected many organs such as pulmonary, gastrointestinal, skin, reproductive, ocular and neuromuscular. The signs and symptoms of hyperthyroidism in sufficient areas of thyroid hormones are fatigue, tremor, sweating, polydipsia, heat intolerance, weight loss, anxiety and palpitations [31-32]. In Graves's disease the common signs and symptoms are ophthalmopathy, thyroid dermopathy and thyroid acropathy. Also the signs and symptoms of nodular goiter are dysphagia, Globus sensation and tracheal compression [33].

Different clinical complications are related to some factors such as gender, age groups, etiology, length of disease and comorbidities. The patients with older age groups have fewer symptoms than the younger age groups but they are sensitive to develop cardiovascular problems [21, 31-32, 34]. Atrial fibrillation is more common in hyperthyroid patients than normal subjects [35-36]. In hyperthyroidism patients the presence of atrial fibrillation is a potential risk factor for congestive heart failure [37]. The high level of mortality has been reported in hyperthyroidism patients with heart problems [38]. Thyrotoxic periodic paralysis is another common problem which is related to hyperthyroidism. The signs and symptoms for paralysis associated with hyperthyroidism are decrease potassium level, muscle paralysis and thyrotoxicosis. Mutation in potassium channels are the main causes of this complication in hyperthyroidism [39-40]. Some other complications which are related to hyperthyroidism are osteoporosis, gynaecomastia, fertility problem and abnormalities in menstrual cycle [41-43].

(d) Subclinical hyperthyroidism

There are some common exogenous and endogenous factors that cause subclinical hyperthyroidism. The most important exogenous causes of subclinical hyperthyroidism are excessive treatment of hypothyroid disorders with L-T4. Another exogenous cause of Subclinical hyperthyroidism is treatment of differentiated thyroid cancer (DTC) with an intentional Thyroid Stimulating Hormone (TSH) suppression [44-46]. In a study reported that 20-40% of patients who take L-T4 have subclinical hyperthyroidism [47].

Endogenous factors which cause the subclinical hyperthyroidism are Grave's disease, toxic multi nodular goiter and toxic adenoma [44-49]. The different studies conducted that the prevalence of subclinical hyperthyroidism which caused by endogenous factors was 0.7-9%. In these studies some factors such as level of iodine intake, the causes of the disease, ages of patients and sensitivity of the tests are used to find the exact level of serum TSH [44-46, 49]. Grave's disease is the most common causes of subclinical hyperthyroidism which is more common in young age group and the areas of excessive iodine intake [49]. In different studies reported that the most common cause of subclinical hyperthyroidism in older and the area of less iodine intake is thyroid autoimmune which causes by toxic multi nodular goiter and toxic adenoma [17, 44-45, 49].

The drugs which are causes subclinical hyperthyroidism and over hyperthyroidism are steroid drugs, dopamine and Amiodarone. Also, the level of TSH concentration might decreases in first trimester of pregnancy. The TSH secretion will decreases in 1-3% of older people with age between 60-80 years due to blunted TSH response to thyroid releasing hormone (TRH). The TSH level in this age group is less than 0.4mU/L. Also the level of free T3 (FT3) will be decreased because of reduction in conversion of T4 to T3 in peripheral tissue (44-45]. The measurement of thyroid stimulating immunoglobulin is a good factor in Grave's disease to suggest the progression of subclinical hyperthyroidism to overt hyperthyroidism [17, 45].

ASSOCIATION OF LIPIDS WITH THYROID DISEASE

Thyroid disease is the most prevalent hormonal disease in the world. Basically thyroid diseases are the conditions which the level of thyroid hormones production being affected. Sufficient amount production of thyroid hormones lead to hyperthyroidism and insufficient amount production of thyroid hormones lead to hypothyroidism. Thyroid hormones play important role in the intermediate metabolisms [50]. Thyroid hormones involve in the synthesis, mobilization and degradation of lipids [47, 50]. Also, Thyroid hormones play important role in lipophagy in the lipid metabolism, mitochondrial quality control and metabolic genes regulation [1]. The degradation effects of thyroid hormones are more predominant than the synthesis effects in lipids [50]. Transport, metabolism and composition of lipids affected by thyroid diseases [2]. The first studies about the association between thyroid diseases and lipids have been done almost 70 years ago (1950s) in humans. On that time eleven hypercholesterolemia subjects were treated with high dose of thyroid [2, 5]. In the first years, scientist recognized that the thyroid hormones may develop the fatty diseases. Also, on that time, researchers defined the connection of thyroid hormones function and cholesterol [3]. In the recent years the association between lipids and thyroid diseases studied and reevaluated with the presence of different data [10]. Update finding approved that the presence of some clinical conditions such as type 2 diabetes mellitus and nonalcoholic fatty liver are associated with alteration in thyroid actions [1]. The importance of cholesterol on thyroid disorders (hyperthyroidism and hypothyroidism) were published by Mason and colleagues in 1930s [3]. Subsequently, many studies were published and conducted that the

concentration of cholesterol, LDL, VLDL, IDL and triglycerides (TGs) might increases in hypothyroidism and decreases in hyperthyroidism. HDL plasma level decreases in hypothyroidism and increases in hyperthyroidism [1-4, 51-53].

Thyroid abnormalities (overt hypothyroidism and subclinical hypothyroidism) have close clinical significance with cardiovascular disease. In overt and subclinical hypothyroidism the risks for cardiovascular disease increases. The thyroid hormone therapy can normalize the lipids values and decreases the risk factor for cardiovascular disease [52-54].

(a) Overt hypothyroidism and lipids

The regulation role of thyroid hormones on lipids metabolism has been well-known [53], thus the link between the overt hypothyroidism and lipids suggested by many data analysis [4, 53]. In a study reported that the lipids profile for 268 subjects with overt hypothyroidism patients were abnormal [2]. In overt hypothyroidism, the level of total cholesterol, LDL suggested in higher level than the normal level. The HDL level (HDL2) may be normal or increased in overt hypothyroidism [2-3]. Usually the serum level of TGs not affected in overt hypothyroidism but often increases in a very small amount. A study in 295 overt hypothyroidism subjects suggested that pure hypercholesterolemia (56%), hypercholesterolemia (34%) and hypertriglyceridemia (1.5%). It means that the total normal lipids in 295 overt hypothyroidism subjects were only (8.5%). [3]. Common causes for secondary dyslipidemia was hypothyroidism, because the cholesterol excretion decreased and the apo B lipoprotein increased in hypothyroidism patients [2]. Hepatic lipase and cholesterol ester transfer protein (CETP) activity decreased in hypothyroidism which increases the level of lipoproteins in plasma [3]. Also, HMG-CoA reductase activity decreases in hypothyroidism. Also, activity of LDL receptors getting decreased thus, resulting in decreasing of LDL and IDL catabolism [4].

In a study the serum level of total cholesterol, LDL cholesterol and triglycerides are increased in clinical hypothyroidism whereas serum level of HDL cholesterol and hepatic lipase activity getting decreased than the normal values. In subclinical hypothyroidism the level of total cholesterol, LDL cholesterol and triglycerides getting increased but the serum level of HDL cholesterol not decreased or increased [55].

In another study, the level of overt thyroid disease is more common in age <20 and subclinical hypothyroidism in age group 20-40 years. This study reported that the levels of all types' thyroid diseases are more common in female than in males. The study reported the direct relation between the serum level of TSH with HDL and LDL in overt hypothyroidism and direct relation between serum levels of TSH with LDL in subclinical hypothyroidism. Total cholesterol and LDL showed higher in hypothyroidism than euthyroid cases. The study reported that the level of total cholesterol and LDL increased with TSH values at the same time [56].

In a different study, reported that the serum level of total cholesterol, LDL-C, VLDL-C and TGs are between reference range in clinical hypothyroidism, subclinical hypothyroidism and euthyroids. On the other hand, the level TGs are higher than normal range in postprandial 8th hour in overt hypothyroidism and subclinical hypothyroidism. Also, the serum level of VLDL-C in overt hypothyroidism is higher than normal range in postprandial 8th hour [57].

(b) Subclinical hypothyroidism and lipids

Subclinical hypothyroidism basically defined by elevation of TSH values than the reference range and maintain the FT3 and FT4 between the normal range whereas the thyroid function starts to fail [2, 58-60]. Whickham and Colorado survey reported that the prevalence of SCH in general population is about 7.5% in women and 3.0% in men [2]. In dyslipidemia subjects about 1-11% of them have SCH [3]. In fact, the relationship between the SCH and dyslipidemia are controversial [6]. Many studies reported that the level of serum TSH, total cholesterol and LDL level increase than the normal range in SCH [2, 53]. Because the high level of TSH in SCH may have the deteriorate effect on lipids levels thus shows change in their values. As well as TSH increases the cholesterol synthesis because of the regulating of HMG-CoA reductase enzyme [53]. In a different study suggested that the level of HDL-C and HDL: TC ratio are decreases in SCH patients than the normal states [2]. A cross sectional studies reported that level of total cholesterol and LDL-C increased in overt hypothyroidism but not in SCH and euthyroid subjects. In another study suggested that, there is no difference in serum LDL-C in SCH and euthyroid subjects, however the TGs level may be increase in a very small amount in SCH subjects. This study reported that increased TSH serum level have link with lipids abnormalities. Usually some studies suggested that the level of Lp (a) and apolipoprotein B may be increased in SCH subjects. The prevalence of SCH in patients with severe lipids abnormalities is more than the euthyroid subjects [6].

Age, sex, some drugs, race, and smoking are the factors which correlate with SCH and lipids. In a study on 1610 subjects with lipids abnormalities the incidence rate of SCH is more common in women with age groups >50 years [3]. The women with SCH the level of lipids may be deteriorate by smoking. Because smoking increases the thyroid dysfunction thus, TSH value increase and FT4 value getting decreased [2]. In the patients with under lowering drugs, there is no association between the SCH and lipids [6].

A study reported that the SCH was 14.7%. The level of HDL was low in children and adolescents age groups with SCH-2(TSH>10mIU/L), which, low HDL is the only lipids abnormalities in this age groups. But the total cholesterol and LDL-C were increased in SCH-2 (TSH>10mIU/L) subjects in adult age groups. This study reported that the level of lipids didn't have any significance differences in SCH-1(TSH <10mIU/L) subjects. The results in this study showed positive correlation between TSH and TC and LDL-C and negative correlation between TSH and TC- and LDL-C [61].

(c) Thyroid Stimulating Hormones and lipids profile

TSH has deleterious effect on serum lipids thus; elevation in TSH values directly might change lipids values. The studies suggested that the TSH has adipogenesis and lipolysis effects. As well as, TSH increase the activity of HMG-CoA reductase thus, increase the cholesterol level in hepatocytes. But some studies suggested that the activity of HMG-CoA reductase doesn't have any link with increase TSH values. There are differences in association between the TSH and lipids level according to obese and sex. There is positive correlation between TSH and Coronary heart disease (CHD). Also the studies reported direct relation between aging, increased TSH and atherosclerotic subjects. TSH has positive correlation with total cholesterol, TGs and LDL-C whereas some studies didn't confirm this correlation. In fact, for association between TSH and lipids needs more researches and studies [62]. Iqbal A. et.al (2001) after a cross-sectional epidemiological study, nested case control study and placebo-controlled double-blind intervention study in 5th Tromoso municipality on 5143 subjects for 1 year reported positive and significance correlation between the TSH and TC and LDL-C in general population. But this result in female didn't have significance correlation according to age and body BMI. This study reported that SCH patients were treated after administration with thyroxine [63].

Rani S. and colleagues reported that the TSH levels are significance higher than the euthyroids subjects. Also the serum level of TC, TGs, LDL, VLDL and HDL are significance higher than euthyroid subjects. In both group females (hypothyroids and euthyroids) TSH has positivie correlation with TC, LDL, TGs and VLDL. But there is no positive correlation between TSH and HDL-C. The study suggested that TSH has very good relationship with lipids than euthyroids [64].

Peng and Yan in 2016 in Wuhan (China) studied the association between thyroid hormones, TSH and lipids profile in 370 depressive subjects in age group >18 years. The study reported that TG and TC/HDL-C ratio higher and HDL-C, FT4 and TSH level in depressive subjects with duration of >3 years than depressive subjects with duration <3years. The study reported TSH has positive correlation with TC and LDL- C and negative correlation FT3 and FT4. Different regression analysis showed significance association between TG, TSH and depressive symptoms duration [65]. Gong Y. et.al (2017) studied on 1003 middle age SCH subjects from Gulou district of Nanjing China during March 2011 to July 2015. The study result reported that the serum TSH has positive correlation with LDL-C [53].

(d) Hyperthyroidism and lipids

The prevalence of hyperthyroidism is lower (2.2%) than hypothyroidism patients in general population. The studies suggested that the prevalence of hyperthyroidism is decreased in hyperlipidemic patients. In a study reported that the prevalence of hypyerthyroidism is 3 out of 248 hyperlipidemic patients. Mostly the synthesis and degradation of lipids increases in hyperthyroidism. In hyperthyroidism the catabolism of LDL

particles increases because of the LDL receptor gene expression increases. In this case the level of TC, LDL-C, ApoB and Lp (a) decreases in both types of hyperthryroidism (subclinical hyperthyroidism and overt hyperthyroidism). The promotor of LDL receptor gene thyroid hormone responsive element (TREs) which allowed F3 to modulate LDL receptor gene expression thus increases the LDL particles catabolism. With increase in LDL catabolism, the level of TC, LDL-C, ApoB and Lp (a) going to be decreased. In hyperthyroidism patients the level of LDL oxidation also be increased. The HDL-C level also decrease because of CETP and HL activity increase in hyperthyroidism. But the level TGs remain unchanged. In hyperthyroidism high degree of lipids degradation occurs in adipose tissue which increases the level of nonesterified fatty acid (NEFA) in blood. As well as the oxidation and ketogenesis also elevated in the liver of hyperthyroidism patients [2-4].

(e) Free Fatty acids and thyroid hormones

There are many protein transporter which are responsible for the uptake of free fatty acids (FFAs) by hepatic cells. These protein transporters are: fatty acid transporter protein (FATPs), liver fatty acid binding proteins (L-FABPs) and fatty acid tranlocase (FAT). Rohit A. et al in a study reported which FATPs are regulated by thyroid hormones receptors. Thyroid hormones increase the uptake of fatty acids from the triglycerides rich lipoproteins. Thyroid hormones regulate the uptake of fatty acid by different tissues [1].

Tikanoja SH. et.al studied the relationship between the level of FT4 and unsaturated free fatty acids in non-thyroidal illnesses (NTI) and chronic renal disease (CRD). This study suggested that the level of FFAs elevated in the NTI subjects than the normal. Among all the FFAs, the level of oleic acid, linolenic acid and linoleic acid affected more than the others. The study reported that the level of FT4 increased and the level of FT3 decreased in NTI subjects. There were positive correlations between the concentration of FFAs and FT4 in NTI subjects. But there weren't any correlation between the unsaturated free fatty acids and FT4 in CRD among those subjects which has normal total FFA and normal FT4 concentration [66]. A different study reported that the level of urinary poly unsaturated free fatty acids such as linoleic acid, arachidonic acid and decahexaenoic acid were decreased in thyroid cancer patients [67].

CONCLUSION AND PERSPECTIVES

Thyroid disease is the most prevalent hormonal disease in the world. Basically thyroid diseases are the conditions which the level of thyroid hormones production being affected. Thyroid hormones play important role in the intermediate metabolisms. Thyroid hormones involve in the synthesis, mobilization and degradation of lipids. The degradation effects of thyroid hormones are more predominant than the synthesis effects in lipids. In the first years, scientist recognized that the thyroid hormones may develop the fatty diseases. In the recent years the association between lipids and thyroid diseases studied and reevaluated with the presence of different data. Update finding approved that the presence of some clinical conditions such as

type 2 diabetes mellitus and nonalcoholic fatty liver are associated with alteration in thyroid actions. Subsequently, many studies were published and conducted that the concentration of cholesterol, LDL, VLDL, IDL and triglycerides (TGs) might increases in hypothyroidism and decreases in hyperthyroidism. HDL plasma level decreases in hypothyroidism and increases in hyperthyroidism. The prevalence of hyperthyroidism is decreased in hyperlipidemic patients and TSH has adipogenesis and lipolysis effects.

REFERENCE

1. Sinha RA, Singh BK, Yen PM. Thyroid hormone regulation of hepatic lipid and carbohydrate metabolism. *Trends in Endocrinology and Metabolism*. 2014; 796: 1-8.
2. Duntas LH. Thyroid Disease and lipids. *Thyroid. Mary Ann Liebert, Inc*. 2002; 12: 287-293.
3. Duntas LH, Brenta G. The Effect of Thyroid Disorders on Lipid Levels and Metabolism. *Med Clin N Am*. 2012; 96: 269-281.
4. Rizos CV, Elisaf MS, Liberopoulos EN. Effects of Thyroid Dysfunction on lipid Profile. *The Open Cardiovascular Medicine Jounal*, 2011; 5: 76-84.
5. Pramfalk C, Pedrelli M, Parini P. Role of thyroid receptor β in lipid metabolism. Biochimica et Biophysica Acta. 2011; 1812: 929-937.
6. Delitala AP, Fanciulli G, Maioli M and Delitala G. Subclinical hypothyroidism, lipid metabolism and cardiovascular disease. *European journal of Internal Medicine*. 2017; 38: 17-24.
7. Parry Z, Macnab R. Thyroid disease and thyroid surgery, Anaesthesia and intensive care medicine (2017), http://dx.doi.org/10.1016/j.mpaic.2017.06.015.
8. Yang MH, Yang FY, Lee DD. Thyroid Disease as Risk Factor for Cerebrovascular Disease. *Journal of Stroke and Cerebrovascular Disease*. 2015; 24: 912-920.
9. Zull D. Thyroid and adrenal disorders, In: Marx JA, Hockberger RS, Walls RM, editors: Rosen's emergency medicine: concepts and clinical practice, edition 7, St. Louis, Mosby; 2010:1658–1671.
10. Unnikrishnan AG, Menon UV. Thyroid disorders in India: An epidemiological perspective. *Indian Journal of Endocrinology and Metabolism*. 2011; 15: 878-881.
11. Tseng FY, Lin WY, Lin CC, et al. Subclinical Hypothyroidism is Associated With Increased Risk for All-Cause and Cardiovascular Mortality in Adults. *Journal of the American College of Cardiology*. 2012; 60: 730-737.
12. Josef E, Miranda PD, Bittencourt MS et al. Subclinical Hypothyroidism is Associated with Higher Carotid Intima-media Thickness in Cross-sectional Analysis of the Brazilian Longitudinal Study of Adult Health (ELSABrasil). Nutrition, Metabolism and Cardiovascular Diseases (2016), doi: 10.1016/j.numecd.2016.06.005.
13. Almandoz JP, Gharib H. Hypothyroidism: Etiology, Diagnosis and Management. *Med Clin N Am*. 2012; 96: 203-221.
14. Chaker L, Bianco AC, Jonklaas J, Peeters R. Hypothyroidism. *Lancet*. 2017; 390: 1550-1562.

15. Jayme JJ, Ladenson PW. Subclinical Thyroid Dysfunction in the Elderly. *TEM*. 1994; 5: 79-86.
16. Gilbert J. Hypothyroidism. *Medicine*. 2017; 45 (8): 506-509.
17. Biondi B. Natural history, diagnosis and management of subclinical thyroid dysfunction. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2012; 26: 431-446.
18. Vanderpump M. Subclinical hypothyroidism: the case against treatment. *TRENDS in Endocrinology and Metabolism*. 2003; 14; 262-266.
19. Unnikrishnan AG, Kalra S, Sahay RK, Bantwal Ganapathi, John M, Tewari N. Prevalence of hypothyroidism in Adults: An epidemiological study in eight cities of India. *Indian Journal of Endocrinology and Methabolism*. 2013; 17: 647-652.
20. Leo SD, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016; 388: 906-918.
21. Devereaux D, Tewelde SZ. Hyperthyroidism and Thyrotoxicosis. *Emerg Med Clin N Am.* 2014; 32: 277-292.
22. Nystrom HF, Jansson S, Berg G. Incidence rate and clinical features of hyperthyroidism in a long-term iodine sufficient area of Sweden (Gothenburg) 2003-2005. *Clinical Endocrinology*. 2013; 78: 768-776.
23. Nordling MA, Bystrom K, Torring O et al. Incidence of hyperthyroidism in Sweden. *European Journal of Endocrinology*. 2011; 165: 899-905.
24. Marino M, Latrofa F, Meconi F, Chiovato L, Vitti P. Role of genetic and non- genetic factors in the etiology of Grave's disease. *Italian Society of Endocrinology.J Endocrinol Invest*. 2014; 38 (3): 283-294.
25. Winsa B, Adami HO, Bergstrom R et al. Stressful life event and Graves's disease. *Lancet*.1991; 338: 1475-1479.
26. Vestergaard P. Smoking and Thyroid disorders- A Meta- analysis. *European Journal of Endocrinology*. 2002; 146: 153- 161.
27. Menconi F. Marcocci C, Marino M. Diagnosis and Calssification of Graves's disease. *Autoimmunity Reviews*. 2014; 13 (4-5): 398-402.
28. McLeod DSA, Cooper DS. The incidence and prevalence of thyroid autoimmunity. *Endocrine*. 2012; 42: 252- 265.
29. Laurberg P, Cerqueira C, Ovsen L et al. Iodine intake as a determinant of thyroid disorders in populations. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2010; 24: 13-27.
30. Fatourechi V, Aniszewski JP, Eghbali GZ, Fatourechi E, Atkinson EJ, Jacobsen SJ. Clinical Features and Outcome of Subacute Thyroiditis in an Incidence Cohort: Olmsted County, Minnesota, Study. *The Journal of Clinical Endocrinology & Metabolism.* 2003; 88 (5): 2100-2105.

31. Goichot B, Caron Ph, Landron F, Bouee S. Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: relationships with age, aetiology and hormonal parameters. *Clinical Endocrinology*. 2016; 84: 445- 451.
32. Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older Subjects with hyperthyroidism Present with a Paucity of Symptoms and Signs: A Large Cross-Sectional Study. *J Clin Endocrinol metab*.2010; 95: 2715- 2726.
33. Bartalena L, Fatourechi V. Extrathyroidal manifestations of Graves' disease: A 2014 update. *J Endocrinol Invest*. 2014; 37 (8): 691-700.
34. Sawin CT, Geller A, Wolf PA et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *The New Journal of Medicine*. 1994; 331: 1250-1252.
35. Bartalena L, Fatourechi V. Extrathyroidal manifestations of Grave's disease. *J Endocrinol Invest*. 2014; 37 (8): 691-700.
36. Biondi B, Kahaly GJ. Cardiovascular involvement in patients with different causes of hyperthyroidism. *J. Nat. Rev. Endocrinol*. 2010; 6: 431-443.
37. Siu Cw, Yeung CY, Lau CP, Kung AWC, Tse HF. Incidene, Clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. *Heart Failure and Cardiomyopathy*.2007; 93: 483-487.
38. Selmer C, Olesen JB, Hansen ML. Subclinical and Overt Thyroid Dysfunction and Risk of All-Cause Mortality and cardiovascular Events: A Large Population Study. *J Clin Endocrinol Metab*. 2014; 99 (7): 2372- 2382.
39. Vijayakumar A, Ashwath G, Thimmappa D. Thyrotoxic Periodic Paralysis:Clinical Challenges. *Journal of Thyroid Research*. Hindawi. Volume 2014; ID 649502:1-6
40. Ryan DP, Da Silva MRD, Soong TW et al. Mutations in Potassium Channel Kir2.6 Cause Susceptibility to Thyrotoxic Hypokalemic Periodic Paralysis. *Cell*. 2010; 140: 88-98.
41. Abe E, Marians RC, Yu w et al. TSH is a Negative Regular of Skeletal Remodeling. *Cell*. 2003; 115: 151-162.
42. Meikle AW. The interrelationships between thyroid dysfunction and hypogonadism in Men and Boys. *Thyroid*. 2004; 14: 17-25.
43. Krassas GE, Poppe K, Glinoer D. Thyroid Function and Human Reproductive Health. *Endorcrine Reviews*. 2010; 31(5): 702-755.
44. Biondi B, Cooper DS. The Clinical Significance of Subclinical Thyroid dysfunction. *Endocrine Reviews*. 2008; 29(1): 76-131.
45. Cooper DS, Biondi B. Subclinical Thyroid disease. *Lancet*. 2012; 379: 1142-1154.
46. Biondi B, Palmieri EA, Klain M, Schlumberger M, Filetti S, Lombardi G. Subclinical hyperthyroidism: Clinical features and treatment options. *European Journal of Endocrinology*. 2005; 152: 1-9.

47. Walsh JP, Bremner AP, Bulsara Mk et al. Thyroid dysfunction and serum lipids: a community-based study. *Clinical Endocrinology*. 2005; 63: 670-675.

48. Wartotsky L. management of Subclinical Hyperthyroidism. *J Clin Endocrinol Metab*. 2011; 96 (1): 59-61.

49. Biondi B, Kahaly GJ. Cardiovascular Involvement in patients with different causes of hyperthyroidism. *Nat. Rev. Endocrinol*. 2010; 6: 431-443.

50. Regmi A, Shah B, Rai BR, Pandeya A. lipid profile in patients with thyroid disorders in Central Nepal. *Nepal Med Coll J*. 2010; 12 (4): 253- 256.

51. Chen Y, Wu X, Wu R et al. Changes in profile of lipids and adipokines in patients with newly diagnosed hypothyroidism and hyperthyroidism. *Sci. Rep*. 2016; 6, 26174.

52. Parie JV, Franklyn JA, Cross KW. Jones SR, Sheppard MC. *Clinical Endocrinology*. 1992; 37: 411-414.

53. Gang Y, Ma Y, Ye Z et al. Thyroid stimulating hormone exhibits the impact on LDLR/LDL-c via up- regulating hepatic PCSK9 expression. Metablosim clinical and experimental. 2017; 76: 32-41.

54. Jung CH, Sung KC, Shin HS et al. Thyroid Dysfunction and Their Relation to Cardiovascular Risk Factors such as lipids Profile, hsCRP, and Waist Hip Ratio in Korea. *The Korean Journal of Internal Medicine*. 2003; 18: 146-153.

55. Shashi A, Sharma N. Lipid Profile Abnormalities in Hypothyroidism. *I. J. S. N*. 2012; 3(2): 354-360.

56. Shah B, Rai BR, Pandeya A. lipid profile in patients with thyroid disorders in Central Nepal. *Nepal Med Coll J*. 2010; 12 (4): 253- 256.

57. Arikan S, Bahceci M, Tuzcu A, Celik F, Gokalp D. Postprandial hyperlipidemia in overt and subclinical hypothyroidism. *European Journal of Internal Medicine*. 2013; 23: e141-e145.

58. Tseng FU, Lin WY, Lin CC et al. Subclinical Hypothyroidism is Associated with Risk for All-Cause and Cardiovascular Mortality in Adults. *Journal of the American College of Cardiology*. 2012; 730-737.

59. Josef E, Miranda PD, Bittencourt MS et al. Subclinical Hypothyroidism is Associated with Higher Carotid Intima-media Thickness in Cross-sectional Analysis of the Brazilian Longitudinal Study Health (ElSA-Brazil. *Nutrition, Metabolism and Cardiovascular Disease*.2016; 26 (10): 915-921.

60. Sato Y, Yoshihis A, Kimishima Y et al. Subclinical hypothyroidism is associated with adverse Prognosis in Heart Failure Patients. *Candadian Journal of Cardiology*. 2018; 34: 80-87.

61. Marwaha RK, Tandon N, Garg MK et al. Dyslipidemia in subclinical hypothyroidism in an Indian Population. *Clinical Biochemistry*.2011; 44: 1214-1217.

62. Delitala AP, Fanciulli G, Maioli M, Delitala G. Subclinical hypothyroidism, lipid metabolism and cardiovascular diseas. *European Journal of Internal Medicine*. 2017; 38: 17-24.

63. Iqbal A, Jorde R, Figenschau Y. Serum lipid levels in relation to serum thyroid-stimulating hormone and the effect of thyroxine treatment on serum lipid levels in subjects with subclinical hypothyroidism: theTromsø Study. *Journal of Internal Medicine* 2006; 260: 53–61.

64. Rani S, Mehta P, Kaur G. Association of thyroid stimulating hormone with lipid profile in hypothyroid females of Mansa District of Punjab (India*). Human Biology Review* (ISSN 227 7 4424). 2017; 6 (1): 10-19.

65. Peng R, Li Y. Low serum thyroid-stimulating hormone levels are associated with lipid profile in depressive patients with long symptom duration. *Journal of Affective Disorders.* 2017; 217: 99-104.

66. Tikanoja SH, Joutti A, Liewendahl B. Association between increased concentrations of free thyroxine and unsaturated free fatty acids in non-thyroidal illness: role of albumin. *Clinica Chimica Acta*. 1989; 179: 33-44.

67. Kim KM, Jung BH, Lho DS, Chung WY, Paeng KJ, Chung BC. *Cancer Letters*. 2013; 202: 173-179.