



**AN ASSESSMENT ON PREVALENCE AND LIPID PROFILE IN GRAVES’
HYPERTHYROIDISM AMONG MADURAI POPULATION (SOUTH INDIAN)**

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ABSTRACT

Graves’s hyperthyroidism is an organ-specific auto-immune disorder. Susceptibility to Graves’ disease (GD) is determined by environmental and genetic factors. The genetic susceptibility to GD is conferred by genes in the human leucocytes antigen (HLA) and Cytotoxic T cell lymphocytes associated molecule –4 (CTLA-4). The current research study is aimed to identify the A/G polymorphism at position 49 in exon - 1 of the CTLA-4 gene and associated complications in GD. For that, a primary level investigation was undertaken to find out the level of T.Chol., TGL, HDL, LDL, VLDL. The study showed that 60 per cent of GD patients had high-level of TGL (223.12±54.61) than control groups (140.44±92.22) and lower level of cholesterol (153± 40.13) than the control group (165.27± 31.97), which might be due to the body inability to utilize and synthesis cholesterol and fat contents, GD patients had low level of HDL (30.61±8.02) than control groups (57.45±12.84) and no significant difference the LDL levels in GD patient (77.84±36.53) between control groups (79.73±39.80).The study shows that the mean value of T3 and T4 are significantly different (p <0.05) more in GD patients than in control group and also shows correlation between the Control group and GD patients.The average TSH value is less in GD patients than in the control group and in this level no correlation between the GD patients than in the control group. A significant correlation is obtained between TGL level and T3, T4, TSH levels. The study is recommended that the further studies will be required to determine a clear association of the CTLA-4 gene polymorphism and associated complications with the remission of GD.

Keywords: ATD, Genetic disease, Gland, Single nucleotide polymorphism, Syndrome and Thyroid.

INTRODUCTION

Thyroid is a butterfly shaped gland composed of two encapsulated lobes, located on either side of the trachea. This is connected by thin isthmus and is composed of spherical thyroid follicles, which contain the hormone colloidal form. T₃ and T₄ are active hormones secreted under the control of TSH. T₃ is 3-4 fold more potent than T₄. It is involved in normal growth and development in children, temperature regulation, metabolism, energy production and intelligence in both children and adults. It also ensures normal growth and development of nervous system (Guyton, 1991). In homeotherms, thyroid hormones regulate Basal Metabolic Rate (BMR) and responsible for the maintenance of high and constant body temperature. Most of the thyroid hormones circulating in the blood are bound to transport proteins such as TBG (Thyroxine Binding Globulin), Thyroxine binding prealbumin TBPA (0-15%) and Albumin (15 – 20%) (Darrasetal., 2004). The normal range of T₄ is 77-155 nmol/L (6-12 µg/dl), T₃ is 1.2-2.8 nmol/L (78 – 182 ng/dl), and TSH is 0.3-4.0mU/L. If the hormone levels are above or below the normal range, it leads to Hyperthyroidism or hypothyroidism (Veeramuthumari *et al.*, 2007). Hypothyroidisms are Hashimoto's thyroiditis and congenital hypothyroidism and Hyperthyroidisms are Graves' disease, postpartum thyroiditis and thyrotoxicosis factitia. Hyperthyroidism also leads to a number of complications like heart problems,

brittle bones (Osteoporosis), eye problems (Graves' ophthalmopathy), red, swollen skin (Graves' disease) and thyrotoxic crisis.

The most common form of hyperthyroidism is Graves' Diseases (GD) an autoimmune disorder in which the antibodies produced by immune system stimulates thyroid gland to produce excess thyroxine. Normally, immune system uses antibodies to help to protect against viruses, bacteria and other foreign substances that invade the body and in GD, occasionally the tissue behind the eyes and the skin of lower legs over the shine gets affected. Though the exact cause for GD is not known, several factors including a Genetic predisposition are likely to be involved (Veeramuthumari, 2007).

GD is an organ-specific heterogeneous autoimmune disorder associated with T-lymphocyte abnormality affecting the thyroid, eyes and skin. GD is a multifactorial disease that develops as the result of a complex interaction between Genetic susceptibility genes and environmental factors (Bednarczuk *et al.*, 2003). The effect of thyroid dysfunction is said to be associated with Low-Density Lipoprotein (LDL) metabolism and High-Density Lipoprotein (HDL) metabolism. HDL has been reported to be normal or decreased in hyperthyroidism, whereas in hypothyroidism HDL has been reported to be increased, normal or even decreased (Tan *et al.*, 1998). Diekman *et al.*, (2000) have also reported that thyroid dysfunction leads to changes in lipoprotein metabolism. Plasma Low-density

lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were increased in hypothyroidism and decreased in hyperthyroidism. Furthermore, clearance of chylomicron remnants is decreased in hypothyroidism. Changes in LDL-C are attributable to altered clearance of LDL-C from plasma by changes in the number of LDL receptors on liver cell surfaces. The promoter of the LDL receptor gene has been reported to contain a Thyroid hormone Responsive Element (TRE). Hence, T3 could modulate gene expression of the LDL receptor. HDL-C metabolism is complex and changes in plasma levels are shown to be due to remodeling of HDL-C particles by hepatic lipase and Cholesterol Ester Transfer Protein (CETP). The activity of both the enzymes have been reported to be decreased in hypothyroidism and increased in hyperthyroidism, correlating with plasma HDL-C level. (Kuivenhoven *et al.*, 1997).

The Triglycerides (TGL) are storage form of lipid found in blood. High levels of TGL are considered as a risk factor for ischemic heart disease and are commonly seen in cases of diabetes, pancreatitis, hyperthyroidism and hypoproteinemas. Under normal circumstances, triglycerides within chylomicrons are stripped of fatty acids as they pass through various tissues (especially adipose and skeletal muscles) (Murray *et al.*, 2003).

The current status reveals the prevalence of hyperthyroidism to be 3.63% and hypothyroidism to be 2.97%; especially the females being more prone to this disorder. So the present study is focused on Graves' hyperthyroidism among females. The major objectives of the study are: To study the prevalence of Graves' disease and to create awareness about the occurrence of thyroidism among scientists, and physicians to promote revival of effective drug development through publishing the work.

METHODOLOGY

More than one hundred fifty patients with thyroid disease were surveyed in the hospital of Dr. K. Kannan Endocrinology Clinic, Madurai. Hundred clinically proved Graves' disease patients within the age group of 20 – 60 were selected, among whom 20 were males and 80 were females and the study concentrated on only female group. Apparently Blending Inheritances in continuous varying traits are due to inheritance that is effect of several genes, which by cumulative effect bring change in magnitude. In the present study, the Body Mass Index (BMI) is analysed in relation to inheritance pattern noted in GD.

18.5 or less	Under weight
18.5 – 24.99	Normal weight
25 – 29.99	Over weight
30 – 34.99	Obesity (Class I)

35 – 39.99	Obesity (Class II)
40 - greater	Morbid obesity

BMI was calculated by using the following formula:

$$\text{BMI} = \frac{\text{Weight in kg}}{2 \times \text{Height in Meter}^2} \text{ (Kg/m}^2\text{)}$$

Result and Discussion

Sudden weight loss, Rapid heartbeat (Tachycardia) – more than 100 beats a minute (irregular heartbeat –arrhythmia, or pounding of heart – palpitations, nervousness, anxiety or anxiety attacks, irritability, tremor, sweating, changes in menstrual patterns, increased sensitivity to heat, changes in bowel patterns, goiter formation, fatigue muscle weakness, difficulty sleeping are the symptoms noted in GD patients. The study group comprised of 100 GD patients taking treatment in the Endocrinology clinic in Madurai among whom females were observed to be more affected (73 per cent) when compared to males (27 per cent). The blood samples were collected from females of age group 20-60 yrs, among whom 34 per cent were in age the group of 20-30 yrs and 33 per cent of them were within the age group of 20-30 yrs.Hence it was observed that the women age of group 20-40 yrs were more affected by GD.

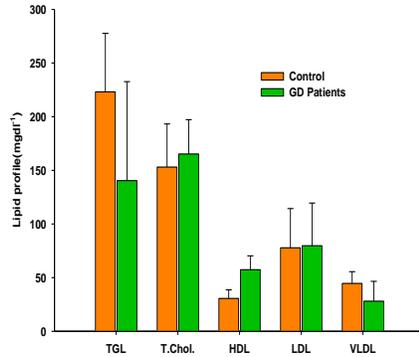
The study reveals that the most of the patients (52.5 per cent) fall in under weight and normal weight (47.5 per cent) categories and in control group most of them (60 per cent) fall

under normal weight, showing that they are healthy. 22.5 per cent in the control group were found to be under weight and 15 per cent were overweight but they don't have any health problems. They have to improve their food. Around 2.5 % are under the conditions of Obese. Positive correlation between BMI and Total cholesterol (r = 0.0844759) is noted and it concedes with earlier observations done by Tan *et al.*, (1998). Hence as the level of total cholesterol increases the BMI also increases. Tan *et al.*, (1998) is taken for the study each patient was matched with a euthyroid control of similar age, sex, and BMI. Blood sample is tested for measurement of lipid. The hyperthyroid patients and their controls were matched for age (27.9±6.4 yrs vs 28.9 ±4.8 yrs) and BMI (20.8±3.1 kg/m² vs 21.9 ±3.2 kg/m²). TSH level was suppressed in all patients. There was a significant rise in BMI and the level of total cholesterol after treatment (p < 0.01). Hence, there is correlation between the BMI, total cholesterol and severity of the GD.

Cholesterol is an important normal body constituent, which is a component of cell membrane and is used in the synthesis of bile acids and steroid hormone. Since cholesterol is water insoluble, most of the serum cholesterol is transported by lipoproteins (Chylomicrons, VLDL, LDL, and HDL). The normal range of cholesterol is 125-200 mg/dl. The present study reveals that most of the patient (Figure 1) had lower level of cholesterol (153± 40.13) than the control group (165.27± 31.97), which might be

due to the body inability to utilize and synthesis cholesterol and fat contents.

Figure 1: Lipid Profile study of Control and GD patients.



Triglycerides are a storage form of lipids found in blood. High levels of TGL are considered as a risk factor for ischemic heart disease and commonly seen in diabetes, pancreatitis, hyperthyroidism and hypoproteinemias (O'Brien *et al.*, 1997). The present study shows that 60 per cent of GD patients had high-level of TGL (223.12 ± 54.61) than control groups (140.44 ± 92.22) (Figure 1). A significant correlation is obtained between TGL level and T3, T4, TSH levels (Figure 2, 3, 4, 5, 6, & 7). The current observation is found to coincide with the report by Murray *et al.*, (2003). The triglycerides stored in adipose tissue are continually undergoing lipolysis (hydrolysis) by a hormone-sensitive lipase to form FFA and glycerol. Hormone sensitive lipase is activated by ACTH, Thyroid hormone, Glucagon etc.(Murray *et al.*, 2003). Therefore in hyperthyroid cases, the levels of thyroid hormone also influence the level of serum / plasma TGL. The current study proves no/less correlation between thyroid hormone and TGL

level (Figure 3, 4, 5, 6,7& 8) because other hormone may take over the lipolysis process.

Figure 2: Correlation between the levels of TGL Vs T3 in control group

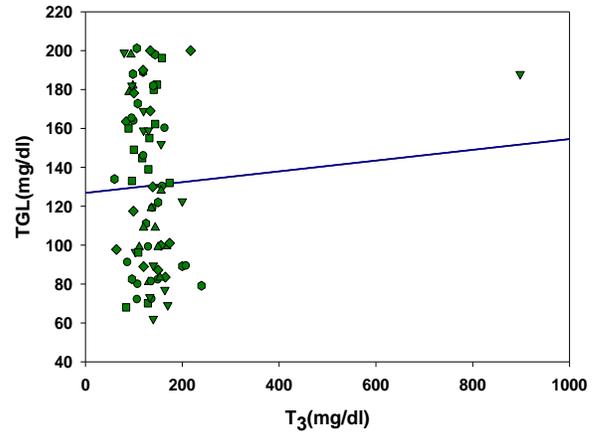


Figure 3: Correlation between the levels of TGL Vs T3 in GD patients.

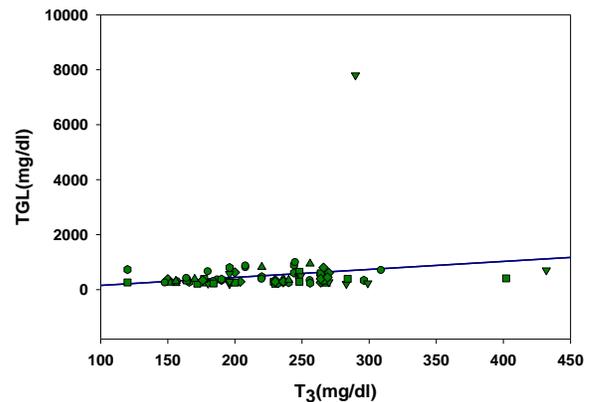


Figure 4 : Correlation between the levels of TGL Vs T4 in control group.

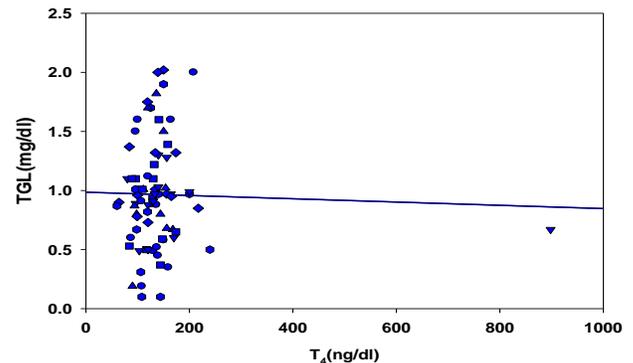


Figure 5: Correlation between the levels of TGL Vs T3 in GD patients.

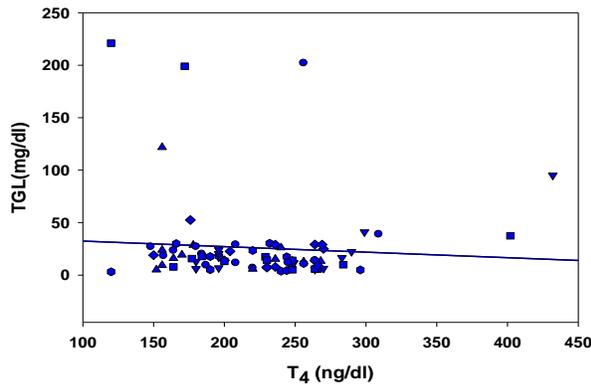


Figure 6: Correlation between the levels of TGL Vs TSH in control group.

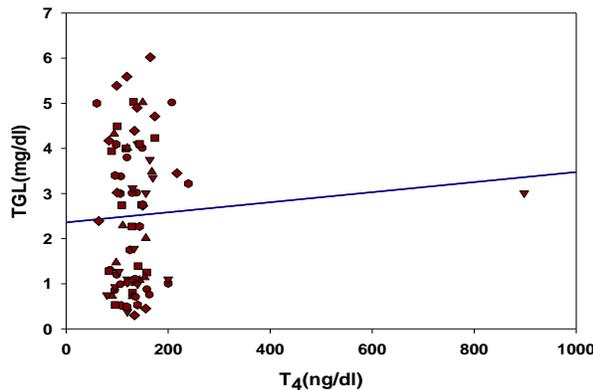
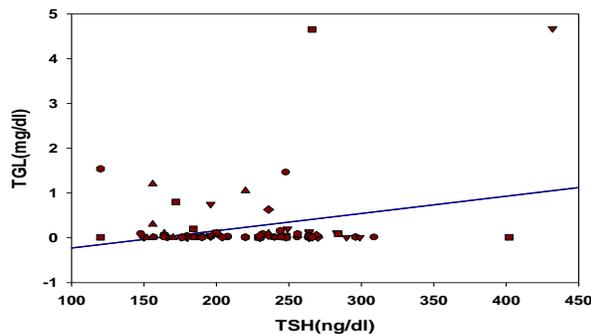


Figure 7: Correlation between the levels of TGL Vs TSH in GD patients



The current study calculated the level of significance using *Student t- test* and it showed that there was a significant difference at $p < 0.05$ level in the level of TGL and VLDL

, whereas T.Chol. and LDL was found to be no significant difference and HDL showed that less significant difference between control group and GD patients.

HDL (“Good cholesterol”) is not secreted into the circulation as a mature lipoprotein but is assembled in the blood from components derived from the intestine, liver, cell membranes and TGL rich lipoproteins during lipolysis (Murray *et al.*, 2003). HDL acts as a scavenger by removing cholesterol from peripheral cells such as smooth muscle and also provides protective benefits from its apparent ability to influence the binding and absorption of LDL by cells such as smooth muscle. Women tend to have better HDL cholesterol than men. In general, an increased risk for heart disease occurs when the HDL level is less than 40mg/dl. More specifically, men are at risk if their HDL is below 37mg/dl and women if their HDL is below 47mg/dl. The HDL level of 60mg/dl or above helps to protect against heart disease. Low HDL may indicate an increased risk of atherosclerotic heart disease (Murray *et al.*, 2003).

LDL carries cholesterol to cells for membrane synthesis and steroid hormone synthesis, via LDL receptor. In healthy human, more than 70% of the LDL circulating in plasma is removed each day through LDL receptor. LDL is sometimes referred to as

“Bad” cholesterol because elevated levels of LDL correlate most directly with coronary heart disease (Murray *et al.*, 2003). LDL cholesterol sticks to artery walls and contributes to plaque build-up. The study has revealed that there is no significant difference between the LDL levels in GD patient (77.84 ± 36.53) and control groups (79.73 ± 39.80). Accelerated catabolism and anabolism of lipid has been reported in hyperthyroidism. Transient elevation of serum lipid levels suggests a more rapid improvement in catabolism than in anabolism of lipid in early stage of the medical treatment (Nishitani *et al.*, 1990). Sucic *et al.*, (1998) have stated that thyroid hormones had only a moderate effect on the metabolism of Lipoproteins.

Heart disease is one of the risk factors for Graves' hyperthyroidism. Heart disease occurs in the condition of low HDL level. It is found that GD patients had low level of HDL (30.61 ± 8.02) than control groups (57.45 ± 12.84) (Figure 2). Hence they are more prone to getting related to heart problems also like atherosclerosis. So GD patients should be aware of their health by frequent checking with physician.

Hence, the study found that, according to several reports suggested that proper treatment of hyperthyroidism depends on recognition of the signs and symptoms of the disease and determination of the etiology. The most common cause of

hyperthyroidism is Graves' disease. Other common causes include thyroiditis, toxic multinodular goiter, toxic adenomas, and side effects of certain medications. The diagnostic workup begins with a thyroid-stimulating hormone level test. When test results are uncertain, measuring radionuclide uptake helps distinguish among possible causes. Graves' disease, toxic multinodular goiter, and toxic adenoma can be treated with radioactive iodine, antithyroid drugs, or surgery. Thyroidectomy is an option when other treatments fail or are contraindicated, or when a goiter is causing compressive symptoms and some new therapies are under investigation.

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