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Relationship of TSH with BMI in subclinical hypothyroid patients

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ABSTRACT

Thyroid hormones (T3 and T4) synthesized by thyroid gland and play an essential role in normal body development and tissue metabolism. Iodine is an essential factor that is required for the synthesis of thyroid hormones. The secretion of thyroid hormones is regulated by Negative feedback mechanism. After reached in blood circulation the majority of T4 and T3 bound with carrier proteins called thyroxine binding proteins (TBG) which shows higher affinity for T4. The common diseases related to thyroid hormones include Hypothyroidism, hyperthyroidism, thyroiditis, goiter, nodes, and tumors of thyroid glands (benign and malignant). Subclinical hypothyroidism also called mild thyroid failure is defined as normal thyroid hormones but mildly elevated TSH (5 – 10 uIU/ml) with no or mild sign and symptoms. The thyroid disorders are more prevalent in females than males. Hypothyroidism is associated with obesity and various studies conducted to find out the relationship between TSH and BMI observed different finding in the particular study. In the present study, a poor positive correlation between TSH and BMI was observed in the total euthyroid subjects. A poor negative association between TSH and BMI in euthyroid males and poor positive (r value – 0.21) relationship was observed in euthyroid females. In Subclinical hypothyroid patients (total, male and female), Poor negative correlation was observed between TSH and BMI. The conclusion of this study is, as TSH increased the BMI will also increase in (mostly females) euthyroid subjects. The Inverse or poor negative correlation was observed within TSH and BMI among euthyroid males and an inverse correlation was noticed in patients with subclinical hypothyroidism.

Keywords: *Thyroid, TSH, subclinical, euthyroid, hyperthyroidism, hypothyroidism.*

1. INTRODUCTION

The Thyroid is an endocrinal, butterfly shaped and biggest gland in neck which makes and stores hormones that help in regulation of blood pressure, heart rate, body temperature and also helps in regulation of growth and rate of chemical reactions (metabolism) in the body. The thyroid gland made up from follicular cells which produce two major hormones of the thyroid gland–T3 (Triidothyronine) and T4 (Tetraidothyronine or Thyroxine) and few parafollicular cells (C–cells) produce hormone called "Calcitonin" which helps in the regulation of calcium homeostasis [1]. Higher amount (80-95%) of T4 is formed but it is biologically less active, T3 is found in less amount (about 5 – 20%) biologically more active than T4 [2]. Thyroid gland cells have receptor site, TSH (Thyroid Stimulating Hormones) secreted by anterior Pituitary linked with these receptors and the cells stimulated to produce and release thyroid hormones; If more T3 and T4 is required to the body then more amount of TSH is produced and if less T4 and T3 required then small amount of TSH produced by pituitary gland [3]. TSH regulates the iodide uptake by sodium/iodide symporters, the steps are necessary for normal thyroid hormone synthesis and secretion [4]. After reached in blood circulation the majority of T4 and T3 bound with carrier proteins -: Thyroxine binding proteins (TBG) having a higher affinity for T4, thyroxine binding prealbumin (transthyretin) and albumin for purpose of transportation [5]. Only a small fraction remains unbound known as free T3 (fT3) and free t4 (fT4) in the circulation, when it reached in to the required tissue it enter inside cells by unique transport channels and cytoplasm is the site where conversions of T4 to T3 take place, mainly in liver, pituitary gland, kidney and peripheral tissue. Normally, about 0.03% T4 and 0.5% T3 were found in unbound form and only free form has the ability to bind with specific hormone receptor in peripheral tissue [6].

Hypothyroidism, Hyperthyroidism, Thyroiditis, Goiter, Nodes and tumor of thyroid gland are the common diseases which are related to thyroid gland [7]. Hypothyroidism is a clinical syndrome resulting from the deficiency of thyroid hormones which leads to slowing down the metabolic processes [8]. The cases of thyroid failure most commonly observed in Women's and the incidence increased with age [9]. Autoimmune chronic lymphocytic thyroiditis is the most common cause of hypothyroidism in Australia. It is commonly seen in diabetic patients [10-11]. It is obesity like pathological condition, associated with lipid metabolism disorders and leads to dislipidemia (one of the major risk factor of coronary diseases) [12]. Hypothyroidism is associated with cardiovascular risk factors and if remain untreated it can lead to atherosclerosis [13]. Subclinical Hypothyroidism SH is defined as abnormal condition which appears with mild elevated TSH level (5 – 10 mIU/L), but normal thyroid hormones concentration with absence of clinical signs and symptoms [14]. It is estimated that the 4.3 – 9% of the general population was affected with SH [15-16]. Effect of subclinical hypothyroidism is not well understood yet but various studies reported that it is associated with high levels of LDL, TC and cardio vascular disease patients [17-18]. Among the children's, autoimmune thyroiditis is the most common cause of SH and diagnosed by elevated levels of Serum Thyroid peroxidise [19-20]. Overt Hypothyroidism Overt Hypothyroidism diagnosed with decreased serum fT4 with increased TSH levels [21]. Overt hypothyroidism

associated with hypercholesterolemia. Previous studies suggested that patients with overt hypothyroidism have more risk of developing atherosclerotic disease. The well documented features of overt hypothyroidism are high levels of apolipoprotein B, LDL cholesterol and total cholesterol [22-24]. Therefore, the catabolism of LDL and IDL is decreased because the activity of LDL receptors decreased and also change in blood pressure [25-27]. An elevated homocystein level is a risk factor for cardiovascular disease and its levels are reported to be increased in overt hypothyroidism [28-30]. Hyperthyroidism Hyperthyroidism also called thyrotoxicosis caused by the overproduction of thyroid hormones [31]. The prevalence found more in women (2%) then men (0.2%) and 15% cases of hyperthyroidism occurs in a patient older than 60 years [32]. In iodine sufficient areas, the prevalence of overt hyperthyroidism is 2 per 1000 and subclinical hyperthyroidism is 6 per 1000 [33]. In general population, the prevalence of hypothyroidism is more than that of hyperthyroidism (2.2%) [34]. Clinical features The symptoms of hyperthyroidism vary according to the Age, amount of T3 and T4 you have and how long your thyroid gland produce excess T3 and T4. It mainly appears with symptoms of sympathetic nervous system. Young patients may suffer from anxiety, tremor and hyperactivity and whereas old age patients might have higher risk for cardiovascular disease related symptoms such as weight loss, dyspnea and atrial fibrillation [35].

2. MATERIALS AND METHODS

The present work was conducted in the Tagore Hospital and Heart Care Centre (Jalandhar). Total 90 volunteers both males and females the age between 17 to 85 years were included in this study. Some import informations were collected from teh patients like age (years), height (cm), weight (kg) and history (such as chief complaints, family thyroid history, blood pressure, Temperature and head and neck examination).

Exclusion criteria include: Smokers and Alcoholic.

Blood Sample collection.

From all the subjects who came for determination of thyroid profile the blood samples with a record of age and sex were collected. By venipuncture method, approximately 5ml blood was collected in a plain vial from all subjects and after centrifugation the serum sample was analyzed for quantitative estimation of thoroid hormones i.e., T3, T4 and TSH levels. The estimation of T3, T4 and TSH in human Serum was done by auto analyzer named as "ADVIA Centaur@CP Immunoassay System" (SIEMENS) based on "Sandwich principle".

Reference Range: T3 - 0.60 - 1.81 ng/ml.
T4 – 3.20 – 12.6 ug/ml.
TSH – 0.35 – 5.0 uIU/ml.

Anthropometrical measurements.

An instrument named as standiometer was used to measure Height (m) and standard weighing machine used for weight. The Body mass index (BMI) for any individual can be calculated by the formula $BMI = {Weight\ (kg)}/{Height\ (m^2)}$

The obesity of a person is classified on teh basis of the BMI calculated. If the values of BMI is <18.5 the person is called as underweight, if the BMI comes between 18.5 to 24.9 the person is of normal weights, if BMI calculated is between 25.0 to 30.0 the person is overweight, in case the BMI comes more than 30.0 the person is obese. According to WHO classification of obesity, if BMI of between 30.0 to 34.9 is class I obese, the BMI of between 35.0 to 39.9 is class II obese and BMI of >40.0 is in class III obese.

Biochemical Analysis: Thyroid Profile Assay (T3, T4 and TSH) performed by using Instrument – ADVIA Centaur@CP Immunoassay System (SIEMENS).

Principle of ADVIA Centaur@CP Immunoassay System (SIEMENS).

Chemiluminescence is a chemical process for the generation of light from the chemical reaction.When two chemical reacts and as a result into a high energy intermediate forms with increased energy, and the intermediates breaks to come back to its ground state and release increased energy inthe form of photon of light. When this process is used along with the immunoassay technique the photon of light released is directly proportional to the concentration of the analyte in a sample.

In Clinical Laboratory Improvement Amendments (CLIA), microplate luminometers is going to be used in place to normal conventional ELISA based colorimetric methods due to its better sensitivity and easy to use. CLIA provides high sensitivity over the conventional colorimetric methods advantages are less incubation time requires and the addition of stopping reagents. The three major components of CLIA are antigen or antibody labeled with horse radish peroxidase (HRP), chemiluminescence substrate mixture containing hydrogen peroxide and teh enhancers. The method is highly sensitive for T3, T4 and TSH estimation.

Principle of T3 immunoassay.

In the case of T3 CLIA, microtiter plate (well) is coated with an specifc quantity of anti-T3 antibody. A fixed measured quantity of patients serum (to be analysed), and a constant amount of T3 conjugated with horseradish peroxidase are added to the microtiter wells. In the incubation, the sample T3 and the conjugated T3 both competes for the limited available binding position on the anti-T3 antibody present on the microtiter well wall. At the end of 60 minutes of incubation at 37°C, the microtiter well will be washed five times with the washing solution for the removal of unassociated T3 conjugates. Then a chemiluminescence substrate solution is mixed and with the help of luminometer the relative light units (RLU) is taken. The RLU intensity is directly proportional to the amount of the enzyme present and inversely proportional to the quantity of unlabelled T3 present in the serum.

With the help of reference sample the T3 comcentration of the serum sample will be estimated.

Principle of T4 immunoassay.

Similar to T3 CLIA, in the case of human T4 CLIA kit also contains a specific quantity of anti-T4 antibody on the wall of micrititer well. A specific amount of patients serum sample (to be analysed) and a fixed amount of T4 conjugated with HRP are mixed in the well. The mixture is incubated for 60 minutes at room temperature. In this 60 minute incubation, the anti-T4 antibody bound to the secondary antibody on the wall of the well. T4 present in the test sample and conjugated T4 competes for the limited available anti-T4 antibody binding sites. At the end of incubation the well is washed 5 times with the washing solution which wash out the unbound T4 cojugates. A chemiluminiscence substrate is mixed and then with the help of luminometer, the RLU is measured. The RLU intensity is directly proportional to the amount of the enzyme present and inversely proportional to the quantity of unlabelled T4 present in the serum. With the help of reference sample the T3 comcentration of the serum sample will be estimated.

Principle of TSH immunoassay.

The human TSH CLIA kit uses two specific monoclonal antibodies against a distnt antigenic determinant of TSH. Wall of microtiter plate well is labelled with the mouse monoclonal anti-TSH antibody whereas HRP is conjugated with the goat anti-TSH antibody. In this case the TSH present in the test sample is allowed to react with the two monoclonal antibodies simultaneously and results in the TSH being sanwitch between two monoclonal antibodies. The complete mixture is incubated for 60 minutes at room temperature and at teh end of incubation teh well is washed five times with teh washing solution to remove unassociated goat anti-TSH antibody conjugates. Then a chemiluminescence substrate solution is mixed and with the help of luminometer the relative light units (RLU) is taken. The RLU intensity is directly proportional to the amount of the enzyme present and inversely proportional to the quantity of unlabelled TSH present in the serum. With the help of reference sample the TSH comcentration of the serum sample will be estimated.

3. RESULTS

The present study was conducted on total of 90 individuals. Both males and females age between 17 – 81 years were included in this study. Firstly, the total data was divided into 3 groups named as: Subclinical Hypothyroid (n= 30), Euthyroid (n=57) and Hyperthyroid include only 3 patients and according to Age, weight (kg), Height (m^2) and BMI the mean ± S.D values were calculated (Table 1). The values (mean ± S.D) of various parameters including thyroid profile, BMI and weight were distributed according to the age groups. The Minimum, Maximum, Average (mean) and S.D values of T3, T4 and TSH were calculated for all 3 groups (S.H, Euthyroid and Hyperthyroid) and placed into the tables (Table 2).

Table 1. The distribution of sample according to age, weight, height and BMI.

Parameter	Subclinical hypothyroid (n=30)	Euthyroid (n=57)	Hyperthyroid (n=3)
Age (Years)	48.6 ±15.8	52.0±12.5	47.3±11.0
Weight (Kg)	74.3±16.7	70.4±11.5	73.3±2.8
Height (m^2)	2.67 ±16.7	2.68±0.3	2.72±0.2
BMI (Kg/m^2)	27.7±5.8	26.3±4.6	27.0±2.9

Table 2. The Minimum, Maximum, Average (mean) and S.D values of T3, T4 and TSH were calculated for all 3 groups (S.H, Euthyroid and Hyperthyroid) and placed into the tables.

	Subclinical Hypothyroidism (n = 30)			Euthyroid (n = 57)			Hyperthyroid (n=03)		
	T3 (ng/ml)	**T4 (ug/ml)**	**TSH (uIU/ml)**	**T3 (ng/ml)**	**T4 (ug/ml)**	**TSH (uIU/ml)**	**T3 (ng/ml)**	**T4 (ug/ml)**	**TSH (uIU/ml)**
Min	0.66	0.41	5.03	0.60	4.4	0.54	1.99	15.1	0.01
Max	1.63	12.5	9.9	1.86	12.5	4.94	4.7	22.1	0.11
Mean	0.97	7.7	7.39	1.07	8.89	2.39	2.92	18.46	0.04
SD	0.25	2.56	1.58	0.29	2.14	1.15	1.53	3.50	0.05

As a comparison between 3 groups, minimum values of T3 (0.60) in Euthyroid, T4 (4.1) in S.H and TSH (0.01) in hyperthyroid were observed. Maximum values of T3 (4.7) and T4 (22.1) in hyperthyroid and TSH (9.9) in SH group were found. The high mean values of T3 (2.92) and T4 (18.46) in hyperthyroid and TSH (29.1) in SH group were observed. Low mean values of T3 (0.97) and T4 (7.7) in SH and low mean TSH (0.04) in hypothyroid group were noticed (Table-3).

For correlation analysis, according to Total, male and female population in euthyroid group the mean and std. dev. values of TSH and BMI were calculated and placed into the table. Correlation coefficient (r value) for total, male and female were calculated in Microsoft Office Excel Worksheet using (Data Analysis) correlation formula. The correlation coefficient (r – value) lies from -1 to +1.

Above tables-3 shows poor Positive relationship between TSH and BMI in euthyroid (Total) that means if one variable increases the other variable also increases or if one decreases and other will also decrease. In males, poor negative correlation (means one variable increases and other variable decreases or vice versa) and in females' poor positive relation was observed in Euthyroid group. In S.H group, poor negative correlation was found in Total, males and females population.

Table 3. Shows the correlation of TSH and BMI in euthyroid and subclinical hypothyroid patients.

	n	TSH (Ulu/ml	BMI(Kg/m^2)	r value	Correlation
Euthyroid subjects					
Total	57	2.39 ±1.51	26.37 ±4.67	0.14	Poor positive
Male	14	2.48 ±1.35	26.01 ±4.29	-0.05	Poor Negative
Female	43	2.36 ±1.09	26.48 ±4.82	0.21	Poor Positive
Subclinical hypothyroid subjects					
Total	30	7.39 ±1.58	27.71±5.86	-0.05	Poor Negative
Male	9	7.36 ±1.64	26.95 ±3.90	-0.27	Poor Negative
Female	21	7.40 ±1.54	28.04 ±6.58	-0.01	Poor Negative

Discussion.

The present study was undertaken to find out the association between TSH and BMI in Subclinical hypothyroid patients and Euthyroid individuals. This study includes total 90 individuals that categorized in three groups (as Euthyroid, Subclinical Hypothyroid and Hyperthyroid) according to their T3, T4 and TSH levels. The total 57 numbers of Euthyroid subjects, Subclinical Hypothyroid include 30 and hyperthyroid include only 3 patients. In our study we found a high prevalence of thyroid diseases in females (n = 66%) than males (n =24%). Various previous studies observed that thyroid hormones can affect the body weight by alter the B.M.R. Some studies show decreased thyroid functions associated with weight gain or obesity and other analysis shows no relation with this regard. The link between body weight and TSH level is especially attractive [36].

In previous studies, it was found that the association between TSH and BMI could be altered by smoking but in recent studies a positive correlation within BMI and TSH was observed in smokers. A study conducted by Knudsen et al. (2005) noticed that little changes in thyroid function are associated with alteration in BMI but the exact mechanism about this association are not clear [37]. The obesity is defined by BMI (>25) and most of the patients were found to obese who came for assessment of thyroid functions in the hospital.

Obesity appears with alterations in lipids parameters which further leads to C.V.D. The decrease functions of thyroid gland are related to obesity and it was suggested that there must be association lies between lipid profile and thyroid hormones. Various studies conducted to find out the relationship between TSH and lipid profile but yet they do not observe any clear relationship [38-39].

A recent study performed by B.A. Laway et al. in 2014 was to evaluate the variations in lipid parameters between Subclinical Hypothyroid and normal individuals were observed the 39 elevated levels of TC, TG and VLDL in patient's with SH. No relationship was observed between HDL and TSH [40].

In present study, the poor positive correlation (r value - 0.14) between TSH and BMI was observed in total Euthyroid subjects. A poor negative association between TSH and BMI in Males and poor positive (r value – 0.21) relationship was observed in Euthyroid females. Suganty et al. (2011) were reported that there was a significant positive correlation between serum TSH and BMI in Euthyroid females [41]. J.J.Deiz et al. also noticed a significant correlation between TSH and BMI in Euthyroid subjects. They conclude that TSH level significantly increased with weight [42].

In SH patients (Total, Male and female), Poor negative correlation was observed between TSH and BMI. This indicates the vice versa relationship lies between TSH and BMI in SH patients. The SH also called mild thyroid failure is defined as a normal thyroid hormone but mildly elevated TSH (5–10 uIU/ml) with no or mild sign and symptoms. The mild symptoms include – weight gain, memory problems and cold intolerance. In the present study the prevalence of weight gain, less sleep and joint pain observed more in SH patients.

Patients with SH have a higher risk of CVD then euthyroid. The occurrence of SH were found significantly higher in the female population. The information about "correlation between TSH and BMI in SH patients" is very less or not well understood. Anjanya Prasad V, et al. in 2013 observed a statistically significant difference between male and female patients with SH. They conclude that the TSH levels were significantly higher in morbidly obese female's patients than in males [42].

The exact mechanism behind the increased TSH in obese person not clears properly and it is more difficult to find mild thyroid failure in obese persons. In obese adults and children's, elevated TSH appeared with enlargement of thyroid gland and hypoechogeneity. Diagnosis of hypothyroidism not only evaluated by ultrasound; the proper diagnosis requires blood test with physical examinations [43-44].

The hypothyroidism is associated with weight gain or obesity and which is the major risk factor for diabetes. Found by various researches that patients with diabetes may have abnormal thyroid functions. A study shows prevalence of 18.3% of SH in patients with Type 2 diabetes mellitus. The prevalence was found more in patients with age more than 50 years [45].

4. CONCLUSIONS

The thyroid hormones play various essential roles in our body and they are essential for normal body functions. They were required to normal regulation of myocardial infarction, pulmonary ventilation, energy homoeostasis, vascular tone, water and electrolyte balance also helps in the normal function of the C.N.S.

Various studies were performed to find out the association between TSH and BMI and each study give a different finding in their study. Based on the data analysis it can interpreted that a poor positive correlation between TSH and BMI and poor negative correlation between TSH and BMI is associated with euthyroid subjects. It indicates that when TSH increases the BMI will also be increased in total and females euthyroid subjects. Inverse or poor negative correlation was observed within TSH and BMI in patients with Subclinical Hypothyroidism.

In the future, further studies regarding to "correlation between BMI and TSH" will defiantly add account in the previous study. Therefore, from the literature available and statistical analysis of the data, it is accepted and state as there is a positive correlation associated between BMI and TSH in Euthyroid subjects (Total and females).

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