Association of Thyroid Status with Metabolic Markers in Young Women of South Indian Origin - A Cross Sectional Study

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ABSTRACT

BACKGROUND
Thyroid hormone is known to regulate metabolisms which are an integral part of normal growth and development. It affects key metabolisms involved in energy storage and expenditure. We wanted to study the correlation of thyroid function test with metabolic markers.

METHODS
After appropriate clearance from Human Institutional Ethics Committee and proper permission from author of article by Dr Sindhu et al, the secondary, blinded data was adopted for this study. This is an observational, cross-sectional retrospective study. Anthropometric measurements were taken, and lipid and thyroid profile were analysed in overnight fasting sample. As per our inclusion and exclusion criteria 120 of 253 subjects included in primary study were recruited in our study. Statistical analysis was done in Microsoft Excel 2007 and SPSS software version 16.0. ATP III criteria were used as a benchmark for metabolic syndrome markers.

RESULTS
Our study suggests that prevalence of subclinical hypothyroidism was higher in young South Indian women and it significantly correlated with the markers of metabolic syndrome like BMI, waist circumference, Low Density Lipoprotein (LDL) and systolic blood pressure. TSH values strongly correlated with BMI and LDL values. FT4 values correlated well with LDL.

CONCLUSIONS
High TSH and lower thyroxine values in blood can be a marker associated with metabolic syndrome. Our study suggests routine screening for thyroid status and lipid profile in young females to categorize them as high risk for cardiovascular mortality and morbidity along with anthropometric measurements. The study can be continued by long term follow up of the study subjects and correlation of these study subjects into mid or old age can give significant information of their cardiac status at that age. Counseling on appropriate diet and lifestyle modification may be beneficial for young people categorized as high risk to reduce the cardiovascular mortality later in life.

KEYWORDS
Thyroid Stimulating Hormone, Free Thyroxine, BMI, Lipid Profile

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BACKGROUND

Thyroid hormone is known to regulate metabolisms, which are the integral part of normal growth and development. Thyroid hormone affects key metabolisms involved in energy storage and expenditure. This happens by both central and peripheral actions thus regulating energy balance in key organs such as brain, brown fat, white fat, muscles, liver and pancreas. Thyroid levels modulate body weight by controlling basal metabolic rate (BMR). This is evidenced by hyper metabolism followed by weight loss due to increased energy metabolism in hyperthyroidism and hypo metabolism followed by weight gain due to reduced energy expenditure in hypothyroidism.[1]

Thyroid hormones (TH) influence anabolic and catabolic pathways of carbohydrates, lipids and proteins. However main mechanisms by which thyroid affects metabolism is by direct or indirect stimulation of sodium / potassium (Na / K) gradient across cell membrane,[2] Calcium (Ca) gradient across cytoplasm and sarcoplasmic reticulum[3] and ryanodine receptors in heart and skeletal muscles[4]. Hence operation of these contributes to increased consumption of ATP.[1] It is well known fact that thyroid hormone maintains BMR mainly by uncoupling mitochondrial oxidative phosphorylation.[1,5] Induction of uncoupling protein 3 (UCP - 3) in the skeletal muscle is believed to play a role in TH induced thermogenesis.[6]

TH is known to regulate cholesterol metabolism by various mechanisms. Main pathway is believed to be increase in the uptake and synthesis of cholesterol by upregulating LDL - R gene directly,[7] and by Sterol regulatory element binding proteins – 2 (SREBP - 2), by its effect on glucose and cholesterol metabolism.[8] TH is also known to reduce body cholesterol by non - LDL receptor mediated pathways. High - density lipoprotein (HDL) assembly and carrying of esterified cholesterol to the liver in reverse cholesterol transport for excretion need ATP - binding cassette transporter A1 (ABCA1). ABCA1 mRNA is induced by SREBP - 2.[9] TH can stimulate both lipolysis and lipogenesis, however the direct effect is lipolysis and lipogenesis occurs only to restore fat stores.[10] TH also plays a key role in maturation of preadipocytes to adipocytes.[11]

T3 is required for normal pancreatic islet cell development, and normal functioning of insulin release and signalling. Thyroid receptor element (TRE) is present at promoter region of glucose transporter (GLUT) - 4, hence T3 has been observed to increase GLUT - 4 mRNA in skeletal muscle thus enhancing glucose uptake.[12,13] Hypothyroidism is associated with lower activity of mitochondria and reduced gluconeogenesis. Severe hyperthyroidism markedly increases the calculated metabolic clearance rate of insulin thus leading to hyperglycaemia.[14]

Regulation of hypothalamic pituitary thyroid axis (HPT) and thermogenesis by bodyweight regulator molecules like adipokines and neuropeptide integrate information on energy availability, storage and utilization thus regulating the appetite, BMR and body weight. Several recent advances have given the insight on factors modifying multiple TH-regulated pathways which help coordinate the signalling pathways which are nutrient feedback at central and cellular level, nutrient nuclear receptor cross talks, ligand activation and adrenergic stimulation. Thyroid hormone analogues are under trial and have shown promising in reducing LDL cholesterol and weight loss.[1]

Cardiovascular mortality remains the leading cause of death in India.[15] Disease manifestation in young age is rare but the risk factors and risk behaviours leading to the development of atherosclerosis begin in childhood. Increasing evidence suggest delay in progression of the disease occurs with reduction of risks.[16] The relationship between thyroid hormone and cardiovascular mortality was established in early 1970s.[17] Owing to the fact that thyroid hormone is intricately involved in maintaining body weight, lipid and carbohydrate metabolism and as per several recent studies including the study by Ross et al has established the association between free thyroxin (FT4) and metabolic syndrome components.[18]

Hence evaluation of Thyroid stimulating hormone (TSH) and FT4 along with routinely done health check tests can help in early isolation of patients with thyroid abnormality there by their treatment can reduce the associated development of cardiovascular disease.

As thyroid abnormality is more common in females, hence we have taken up this study to assess the incidence of obesity, dyslipidaemia, and hypertension and its correlation with thyroid status in our young adult female population.

METHODS

After appropriate clearance from "Human Institutional Ethics Committee" and proper permission from author of an article (Dr Sindhu et al [19]) the secondary, blinded data was adopted for this study. It was an observational, cross-sectional retrospective study. Secondary data analysis from the primary study data was done.[19] Primary study data was collected as follows, all the MBBS students (girls) aged 18 – 25 yrs, studying in our medical college, volunteering for the study were included. Subjects with any chronic illness or thyroid abnormality, on regular medication for thyroid abnormality or acute or chronic illness were excluded from the study. A Questionnaire was made for filling demographic data of the subjects; consent was taken for sample collection. With all aseptic precautions as per our sample collection manual, participant's 3 mL fasting venous sample was collected in SST (serum separator tubes) yellow vacutainer of Becton, Dickinson and Company (BD).[20] Samples were transported to Biochemistry laboratory and centrifuged to separate the serum. Serum sample was used to analyse free thyroxine and thyroid stimulating hormone by Enzyme linked immune fluorescent assay (ELFA) in Vidas autoanalyzer[21] and lipid profile tests like total cholesterol values by cholesterol oxidase peroxidase method, Triglycerides values by glycerol kinase method, and High density lipoprotein (HDL) values by phosphotungstic acid / $MgCl_2$ method was done in Vitros 5.1 FS instrument.[22] Low density lipoprotein (LDL) values and very low density lipoprotein (VLDL) values were calculated using Friedwald equation as per our standard protocol.[22]

Statistical Analysis

As per our inclusion and exclusion criteria, 120 of 253 subjects included in primary study were recruited in our study. Statistical analysis was done in SPSS software version 16.0 and Microsoft excel 2007. ATP III criteria,[23] were used as a benchmark for metabolic syndrome markers. Values of the age, height, weight, waist circumference, Body mass Index (BMI), thyroid stimulating hormone (TSH), free thyroxine (FT4), Total cholesterol, LDL, VLDL HDL, serum triglyceride values were expressed as mean ± SD and prevalence of thyroid status in the study subjects were expressed as percentage. Comparison of metabolic syndrome markers between Euthyroid and Subclinical hypothyroid subjects was done using Student t test, as all parameters were continuous variables and showed normal Gaussian distribution. Pearson's correlation was used for correlating TSH and FT4 with parameters of lipid profile.

RESULTS

Parameters	Biological Reference Interval	Mean ± SD
Age (years)	---	20.96 ± 1.57
Height (cms)	---	158.13 ± 7.45
Weight (Kg)	---	59.76 ± 13.37
Waist circumference (cms)	---	87.2 ± 10.64
BMI	18.5 - 22.9	23.88 ± 5.024
Systolic BP (mmHg)	90 -120	111.2 ± 12.51
Diastolic BP (mmHg)	< 80	74.48 ± 8.21
Pulse (beats /min)	72	80.24 ± 8.82
Total cholesterol (mg / dL)	< 200 desirable	151.8 ± 26.11
Serum Triglycerides (mg / dL)	<150 desirable	76.96 ± 32.49
HDL (mg / dL)	> 40 desirable	47.4 ± 8.85
LDL (mg / dL)	<100 desirable	92 ± 25.91
VLDL (mg / dL)	25 - 40	15.50 ± 6.42
FT4 (pmol / L)	9 - 24	15.80 ± 2.44
TSH (µIU / mL)	0.25 - 5.5 µIU / mL	2.5 ± 1.74

Table 1. Baseline Biochemical Parameters and Anthropometry of the Study Subjects

BMI - Body mass index, BP - Blood pressure, HDL - high density lipoprotein, LDL - Low density lipoprotein, VLDL - Very low density lipoprotein, FT4 - Free Thyroxine, TSH - Thyroid stimulating hormone.

Classification Using BMI	No. of Participants	Percentage
Underweight	12	8.39 %
Normal	53	43.09 %
Overweight	19	15.83 %
Obese	39	32.50 %

Table 2. Prevalence of Obesity in Young Women of South Indian Origin

A significant portion of our study subjects (48.33 %) were found to have BMI above the accepted value.

	Numbers	Prevalence in our Study Subjects
Sub-clinical Hyperthyroidism	2	1.66 %
Euthyroid	107	89.16 %
Sub-clinical Hypothyroidism	11	9.16 %
Total number of study subjects	120	-

Table 3. Thyroid Status among the Study Subjects

Prevalence of subclinical hypothyroidism (9.16 %) was high in our study subjects.

Parameters	Euthyroid Mean ± SD	Subclinical Hypothyroid Mean ± SD	t Value	P Value
Age (Years)	20.87 ± 1.6	21.45 ± 1.5	-1.17	0.12
Waist circumference (cms)	85.33 ± 8.87	103.9 ± 11.5	-6.42	<0.001**
BMI	23.07 ± 4.13	30.64 ± 5.57	-5.58	<0.001**
Systolic BP (mmHg)	110.78 ± 12.88	115.09 ± 8.78	-1.08	0.14
Diastolic BP (mmHg)	74.05 ± 7.8	78.54 ± 11.52	-1.73	0.04*
Total cholesterol (mg / dL)	151.9 ± 25.8	156.5 ± 26.83	-0.55	0.29
Serum Triglycerides (mg / dL)	77.02 ± 33.24	80.72 ± 26.83	-0.35	0.36
HDL (mg / dL)	47.91 ± 8.74	44.27 ± 9.2	1.3	0.9
LDL (mg / dL)	88.61 ± 23.77	125 ± 23.4	-4.84	<0.001**
VLDL (mg / dL)	15.54 ± 6.58	16.18 ± 5.4	-0.3	0.37
FT4 (ng / dL)	15.83 ± 2.32	14.22 ± 1.43	2.24	0.98
TSH (µIU / mL)	2.11 ± 1.03	6.79 ± 1.4	-13.78	<0.001**

Table 4. Comparison of Metabolic Syndrome Markers between Euthyroid and Subclinical Hypothyroid Subjects (Student t Test)

* P value<0.05, ** P value<0.001 is statistically significant

Statistically significant differences for waist circumference, BMI, diastolic BP, LDL cholesterol were observed euthyroid and subclinical hypothyroid study subjects.

Parameters	TSH Pearson Correlation	TSH P Value	FT_4 Pearson Correlation	FT_4 P Value
BMI	0.278	0.02*	-0.28	0.762
Waist circumference	0.367	0.00**	-0.72	0.43
Total cholesterol (mg / dL)	0.169	0.65	-0.142	0.122
Serum Triglycerides (mg / dL)	0.071	0.438	-0.126	0.170
HDL (mg / dL)	-0.057	0.537	0.039	0.676
LDL (mg / dL)	0.367	0.00**	-0.216	0.019*
Systolic BP (mmHg)	0.014	0.881	-0.066	0.472
Diastolic BP (mmHg)	0.149	0.103	0.035	0.706

Table 5. Pearson's Correlation of TSH and FT_4 with Metabolic Syndrome Markers

* p value<0.05, ** p value<0.001 is statistically significant

TSH values positively correlated with BMI, Waist circumference and LDL values and it was found to be statistically significant. FT4 values negatively correlated with LDL values and it was found to be statistically significant.

DISCUSSION

Thyroid hormone is an important hormone for regulating carbohydrate and lipid metabolism. ATP III criteria for metabolic syndrome,[23] takes into account the markers of abnormal carbohydrate metabolism like fasting blood glucose, and lipid metabolism like serum lipid profile values especially triglycerides and HDL levels. Both lipid and carbohydrate metabolisms in the body depict the body mass index (BMI) and waist circumference. Waist circumference too is an important marker as per ATP III criteria. The last criterion is blood pressure.

Our study suggests that prevalence of subclinical hypothyroidism was higher in young South Indian women,[19] and it significantly correlated with the markers of metabolic syndrome like BMI, Waist circumference and LDL.

As per ATPIII criteria for metabolic syndrome, [23] the upper cut-off for waist circumference for cardiovascular risk in females is< 88 cm, when euthyroid subjects were compared with subclinical hypothyroid study subjects, subclinical hypothyroid subjects showed a mean waist circumference of 103.9+11.5 cms, which is well above the acceptance criteria. Similar differences were observed for

other metabolic syndrome parameters like BMI, LDL, and systolic BP. Subjects with subclinical hypothyroidism subjects showed mean BMI and LDH of 30.64 ± 5.57 and 125 ± 23.4 as compared to 23.07 ± 4.13 and 88.61 ± 23.77 respectively in euthyroid subjects.

TSH values positively correlated with BMI, Waist circumference and LDL values and this correlation was found to be statistically significant. FT4 values negatively correlated with LDL values with statistical significance.

Study done by J de J Gardun˜O - Garcia,[24] concluded that metabolic syndrome markers were not significantly different in euthyroid and subclinical hypothyroid study subjects. However their study showed positive correlation of TSH values with total cholesterol, triglycerides, and waist circumference and FT4 values showed a positive correlation with HDL cholesterol and a negative correlation with fasting insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA - IR) and waist circumference. These were not statistically significant because similar differences were seen also in subjects with euthyroid status. These findings are similar to the findings in our study. Few other studies, like done by Demidova,[25] and by Uzunlulu,[26] also suggest significant negative correlation of thyroid status in the body with metabolic syndrome markers there by supporting the finding of our study. Prevalence of Polycystic ovarian disease (PCOS) was found to be 11.96 % among Indian adolescent females, and PCOS is also known to have strong correlation with metabolic syndrome. Early identification and treatment of women with such abnormality can even prevent associated reproductive complications.[27]

CONCLUSIONS

Thyroid hormones are intricately involved in maintaining energy storage and expenditure. High TSH and lower thyroxine values in blood can be a marker associated with metabolic syndrome. Higher prevalence of subclinical hypothyroidism and obesity in young women from south India was found than previously thought. Our study suggests routine screening for thyroid status and lipid profile in young especially those with higher body mass index and / or high waist circumference. They should be categorised as people with high risk for cardiovascular mortality and morbidity.

Long term follow-up and correlation of these study subjects up to mid or old age can give significant information regarding their cardiac status at that age. Counseling on appropriate diet and lifestyle modifications, at an appropriate age, may be beneficial for young people who have been categorized as high risk and it can reduce the cardiovascular mortality later in life.

The limitation of the study was that the possibility to modify the study plan was limited as the data was secondary to another larger study.[19] As plasma glucose values of the study subjects were not available, the correlation of TSH and FT4 could not be done with all the parameters of metabolic syndrome.

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REFERENCES

[1] Mullar R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev 2014;94(2):355-382.
[2] Ismail-Beigi F. Regulation of Na^+, K (+) - ATPase expression by thyroid hormone. Semin Nephrol 1992;12(1):44-48.
[3] De Meis L. Role of the sarcoplasmic reticulum Ca^{2+}-ATPase on heat production and thermogenesis. Biosci Rep 2001;21(2):113-137.
[4] Jiang M, Xu A, Tokmakejian S, et al. Thyroid hormone - induced overexpression of functional ryanodine receptors in the rabbit heart. Am J Physiol Heart Circ Physiol 2000;278(5):H1429-H1438.
[5] Botham KM, Mayes PA. The respiratory chain & oxidative phosphorylation. Chap - 13. Harper's Illustrated Biochemistry. 28th edn. USA: 2009: p. 103-112.
[6] Flandin P, Lehr L, Asensio C, et al. Uncoupling protein - 3 as a molecular determinant of the action of 3,5,3'-triiodothyronine on energy metabolism. Endocrine 2009;36(2):246-254.
[7] Lopez D, Socarras AJF, Bedi M, et al. Activation of the hepatic LDL receptor promoter by thyroid hormone. Biochim Biophys Acta 2007;1771(9):1216-1225.
[8] Goldstein JL, DeBose-Boyd RA, Brown MS. Protein sensors for membrane sterols. Cell 2006;124(1):35-46.
[9] Wong J, Quinn CM, Brown AJ. SREBP-2 positively regulates transcription of the cholesterol efflux gene, ABCA1, by generating oxysterol ligands for LXR. Biochem J 2006;400(3):485-491.
[10] Oppenheimer JH, Schwartz HL, Lane JT, et al. Functional relationship of thyroid hormone-induced lipogenesis, lipolysis and thermogenesis in the rat. J Clin Invest 1991;87(1):125-132.
[11] Obregon MJ. Thyroid hormone and adipocyte differentiation. Thyroid 2008;18(2):185-195.
[12] Torrance CJ, Devente JE, Jones JP, et al. Effects of thyroid hormone on $GLUT_4$ glucose transporter gene expression and NIDDM in rats. Endocrinology 1997;138(3):1204-1214.
[13] Weinstein SP, Watts J, Haber RS. Thyroid hormone increases muscle/fat glucose transporter gene expression in rat skeletal muscle. Endocrinology 1991;129(1):455-464.
[14] Randin JP, Tappy L, Scazziga B, et al. Insulin sensitivity and exogenous insulin clearance in Graves' disease. Measurement by the glucose clamp technique and continuous indirect calorimetry. Diabetes 1986;35(2):178-181.

[15] Prabhakaran D Jeemon P, Roy A. Cardiovascular diseases in india current epidemiology and future directions. Circulation 2016;133(16):1605-1620.
[16] Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011;128(Suppl 5):S213-S256.
[17] Heinonen OP, Gordin A, Aho K, et al. Symptomless autoimmune thyroiditis in coronary heart disease. Lancet 1971;1(7754):785-786.
[18] Ross A, Bakker SJL, Links TP, et al. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. Journal of Clinical Endocrinology and Metabolism 2007;92(2):491-496.
[19] Sindhu R, Vastrad S, Vinay AV, et al. Subclinical thyroid disorders and its association with dyslipidemia at a tertiary care institute. Journal of Evidence Based Medicine and Healthcare 2019;6(2):77-81.
[20] Becton M, Dickinson F. Becton, Dickinson and Company. https://www.bd.com/en-us/offerings/capabilities/specimen-collection/blood-specimen-collection/venous-collection/bd-vacutainer-blood-collection-tubes.
[21] https://www.biomerieux-diagnostics.com/vidasr-thyroid-panel.
[22] Vitros Microslide - Instructions for use manual, Orthoclinical diagnostics, Medical diagnostics New Jersey, United States. 2009.
[23] Braunwald E, Loscalzo J. The metabolic syndrome. Chapter - 236. Harrison's Principles of Internal Medicine. 17th edn. USA: McGraw-Hill Publication 2008.
[24] De Jesus GGJ, Alvirde-Garcia U, Guadalupe Lopez-Carrasco G, et al. TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. European Journal of Endocrinology 2010;163(2):273-278.
[25] Demidova Tiu, Galieva OR. The role of thyroid hypofunction in development of metabolic syndrome. Endocrine Journal 2007;54:71-76.
[26] Uzunlulu M, Yorulmaz E, Oguz A. Prevalence of subclinical hypothyroidism in patients with metabolic syndrome. Terapevticheskii Arkhiv 2009;81:69-73.
[27] Singh A, Vijaya K, Laxmi KS. Prevalence of polycystic ovarian syndrome among adolescent girls: a prospective study. Int J Reprod Contracept Obstet Gynecol 2018;7(11):4375-4378.