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Original Research Article

Correlation of T3, T4 and TSH with lipid indices in obesity

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ABSTRACT

Background: Aim was to study the influence of Thyroid hormones on lipid indices in obese individuals. Thyroid dysfunction is a common occurence in South India. Increased accumulation of fats is a common feature of obesity and hypothyroidism.
Methods: The study was undertaken at GGH, Guntur and 150 Obese individuals with BMI of >30 were recruited. They are classified into 3 groups based on thyroid profile - Euthyroid (N=77), hypothyroid (N=45)and hyperthyroid (N=28). Their fasting venous blood samples were analysed for thyroid profile, lipid profile, FBS and creatinine. Anthropometric data like height, weight and abdominal circumference was recorded. Lipid indices, atherogenic index of plasma (AIP), Castelli's Risk Index (CRI) 1 and 2, small dense LDL (sdLDL), Atherogenic coefficient (AC) and BMI were calculated.
Results: All the 3 groups showed female preponderance. In hypothyroid cases TSH, T3 and T4 showed significant correlation with lipid parameters (p value<0.0001) and with lipid ratios TSH and T4 significantly elevated (p value <0.00001). There was significant correlation of TSH with TC, TG and LDL between hypothyroid, hyperthyroid and euthyroid cases($p<0.0001$). Spearman's Rho correlation analysis showed negative correlation of Lipid ratios with T3, T4 and TSH in all 3 groups.($r\leq1.0$). Whereas multiple regression analysis of lipid ratios in all 3 groups with TSH as dependent variable demonstrated positive relation with sdLDL ($p<0.01$).
Conclusions: Assessment of thyroid function is mandatory in all obese individuals to predict complications especially cardiovascular disease.

Keywords: Lipid indices, Obesity, Thyroid profile

INTRODUCTION

Obesity is a growing health problem in India and worldwide. Changes in lifestyle, urbanization, stress were risk factors increasing the incidence and prevalence of Obesity. According to National Family Health Survey, India-5 (2019-20) phase-1 in the state of Andhra Pradesh 36.3% females and 31.1% males were obese or overweight.[1] 44.4% females, 37.7% males urban population and 32.6% females, 28.0% males residents of rural areas have BMI≥25.0 kg/m^2. BMI greater than 30kgs/m^2 was considered obese. BMI was calculated using the formula weight in Kgs/ height (Mt)^2. The National Cholesterol Education Programme (NCEP) defines dyslipidemia as follows.[2]

Hypercholesterolemia- serum total cholesterol >200mgs/dl, hypertriglyceridemia - serum triglycerides >150mgs/dl, Low HDL-C- serum high density lipoproteins < 40mgs/dl and elevated LDL-C - serum low density lipoproteins > 130mgs/dl.

The normal range of thyroid hormones is T3: 0.87-1.78 mgs/ml, T4: 4.82 - 15.65mgs/dl, TSH: 0.4 - 5.6 IU/ml. Thyroid dysfunction was associated with dyslipidemia. Lipid indices were being considered better predictors of risk of cardiovascular disease rather than individual lipid parameters. The lipid indices were calculated using the following formulae. Atherogenic Index of Plasma (AIP) = Log (TG/HDL-C).

- Castelli's Risk Index - (CRI-1) = TC / HDL-C
- Castelli's Risk Index - (CRI-2) = LDL/ HDL-C
- Small dense LDL-C (sdLDL) = TG / HDL-C 3
- Atherogenic Coefficient (AC) = (TC-HDL-C) / HDL-C

The following are the abnormal values of lipid ratios for cardiovascular risk: AIP>0.1, CRI-1>3.5 in males and>3.0 in females, CRI-2>3.3, AC>3.0, and sdLDL>4.04.

Inspite of the fact that LDL-C is the single atherogenic fraction with risk of CVD, residual and equally important risk factors to be kept in mind are Hypertriglyceridemia, reduced HDL-C and small dense LDL. Non-HDL-C (TC-HDL-C) fraction represents remnant Lipoproteins which increase inflammatory markers and atherosclerosis.[5] Non HDLC represents ApoB containing lipoproteins.It is found that proinflammatory markers remain elevated despite statin therapy.

Thyroid hormones modulate carbohydrate, protein and lipid metabolism. Lipid metabolism is mainly regulated by thyroid hormones.[6] Cholesterol is synthesised in liver and other tissues and transported in circulation in the form of Lipoproteins (Lps). Among the subfractions of Lps low density lipoproteins (LDL-C) are susceptible to oxidation and are atherogenic. Cholesterol esters are synthesised by Lecithin Cholesterol Acyl Transferase (LCAT). Hormone sensitive Lipase (HL) regulates hydrolysis of High-Density Lipoproteins (HDL) and Lipoprotein Lipase (LPL) catabolizes Triglycerides (Tgs). The activity of LCAT, HL and LPL regulated by thyroid hormones. In obesity TSH and T4 were found to be elevated and interconversion of T3 and T4 was found to be high in Obesity as a protective mechanism to combat fat accumulation by increasing energy expenditure as well as basal metabolic rate.[7-10]

Presently lipid indices were being considered as better markers of risk of cardiovascular disease rather than individual lipid fractions especially when they are virtually within normal limits. AIP acts as a surrogate marker of apolipoprotein (B), and it accurately reflects the status of atherogenic LDL-C and antiatherogenic HDL-C. Castelli's risk index -I (TC/HDL-C) indicates intima-media thickness in carotid arteries and higher values are associated with coronary plaque formation.[11]

Low density lipoprotein has 3 subclasses according to size and density. Large (buoyant) - 26.0-28.5 nm, Intermediate - 25.5 - 26.4 nm and small, dense LDL-24.2 -25.5 nm were 3 subclasses.[12] These phenotypes can be seggregated by HPLC, GGE (Gradient Gel Electrophoresis) and NMR (Nuclear Resonance Imaging), sdLDL was calculated using the formula suggested by Palazy et al.[3] Atherogenic coefficient is ratio of TC- HDLc/HDL-C.

METHODS

The present study was a case control study undertaken at GGH, Guntur, a tertiary care hospital from August 2019 to February 2020. The individuals were attending medicine OPD for treatment of obesity. 150 Obese subjects with BMI of >30 were selected for the present study. Institutional ethical committee approval was taken for the study. Depending on TSH and T4 values the study group was classified into 3 groups viz; Euthyroid (77), Hypothyroid (45) and Hyperthyroid (28). Informed oral consent was obtained from them to participate in the study. Anthropometric data was recorded - height, weight, abdominal circumference, waist circumference. Their fasting venous blood samples were collected under asceptic conditions. The blood samples were analysed for FBS, urea, creatinine, Triglycerides (TG), Total Cholesterol (TC), High Density Lipoproteins (HDL), Total Triiodotyronine (T3), Total Thyroxine (T4) and Thyroid Stimulating Hormone (TSH). FBS, Urea, creatinine and lipid profile was done on Johnson and Johnson Vitros 250 dry chemistry analyser and Thyroid profile was done on Beckman Coultier Access 2 - Chemiluminiscence assay.

Low density lipoproteins and very low density lipoproteins were calculated as follows using Friedwald's formula.[13]

VLDL=TG/5 and LDL=TC - HDL- TG/5.

Inclusion criteria

Obese individuals with BMI of >30 with FBS value <126 mgs/dl, urea (20-40 mgs/dl) and creatinine (0.6-1.2 mgs/dl). All the individuals were normotensive.

Exclusion criteria

Past history of acute MI, known diabetics on treatment, individuals on medication like OC Pills, antiepileptics or antipsychotics. Other endocrine disorders were ruled out by taking relevant history.

Statistical analysis

Done by NNCSS 2021 v21.0.2. Data was expressed as Mean±Standard Deviation (SD). Statistical comparison of means between the 3 groups and within the same group were done by one way ANOVA (Analysis of Variance). Spearman's Rho correlation was done to study the association between parameters. Area under curve (AUC)

was done between the 3 groups for lipid ratios to understand their significance and interrelation. P value of <0.05 was considered as statistically significant.

RESULTS

Mean, SD of biochemical parameters and Lipid ratios was shown in Table 1. Females were included more in the study than males. Only marginal difference was observed between the mean values of euthyroid, hypothyroid and hyperthyroid groups. One way ANOVA showed significant elevation of T4, TSH, TG, TC, HDL and LDL within the same group as well as amongst the three groups. Table 2 and 3 (p value<0.00001). Among atherogenic Lipid ratios AIP, CRI-1, CRI-2, sdLDL and Ac correlated significantly with T4 and TSH within hypothyroid obese individuals Table 2 (p<0.00001) but T3 did not show significant elevation with lipid ratios (f=0.816 and p=0.521). Statistically negative correlation was observed between TSH, T3 and T4 and lipid ratios in all 3 groups according to Spearman's Rho Correlation Table 4 with r value less than 1.

Area Under Curve (AUC) of AIP was not significant in hyperthyroid/hypothyroid obese individuals compared to euthyroid individuals (0.6). Whereas AUC of CRI-1, CRI-2 and sdLDL was significant in hyperthyroid /hypothyroid individuals compared to euthyroid individuals (>7.5; 6 and > 4.5 and >7.5 respectively). Atherogenic coefficient did not show significant elevation in hyperthyroid obese individuals (<0.5) compared to hypothyroid obese individuals (>6.5). Means, CRI-1, CRI-2 and sdLDL ratios would identify the risk of atherogenesis irrespective of thyroid status in obese individuals. AIP (-10 log of TG and HDL) and AC (a ratio of (TC-HDLc)/HDLc) in this study did not signify the risk of atherogenicity in euthyroid, hypothyroid and hyperthyroid obese individuals. T3, T4 and TSH correlated negatively with AIP, CRI-1 and 2, sdLDL and AC in all 3 groups (r<1.0) Table 4 except positive correlation of T4 with CRI-1 and 2 and AC in Euthyroid subjects (p value<0.037, <0.01 and < 0.035 respectively) Table 4.

Significant correlation was not observed in this study between T3, T4 and TSH and lipid ratios whereas the study done by Zhenjiang et al established highly significant positive correlation in hypothyroid individuals.[15] Multiple regression analysis was done considering TSH as dependent variable and lipid ratios as independent variables. It was found that sdLDL was associated with TSH in euthyroid, hypothyroid and hyperthyroid groups (p value<0.01; <0.007, <0.01). Table 5 whereas other ratios correlated poorly with TSH.

Area Under Curve (AUC) of AIP was 0.5 in hyperthyroid, hypothyroid vs euthyroid cases and that of CRI-1 (Figure 2) was >7.5; CRI-2 (Figures 3) was 4.0 and 6.0; sdLDL (Figure 4) was >7.5 and AC (Figure 5) was <0.5 and > 6.5 at 95% confidence interval. This is in accordance with the study conducted by Nimmanapalli et al.[16]

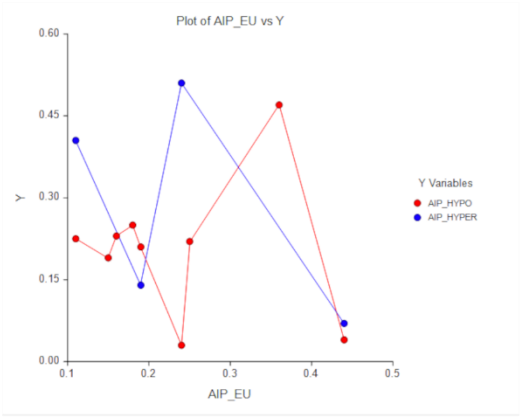

Figure 1: AUC-AIP-X-axis (euthtyroid cases), Y-axis hypothyroid and hyperthyroid cases.

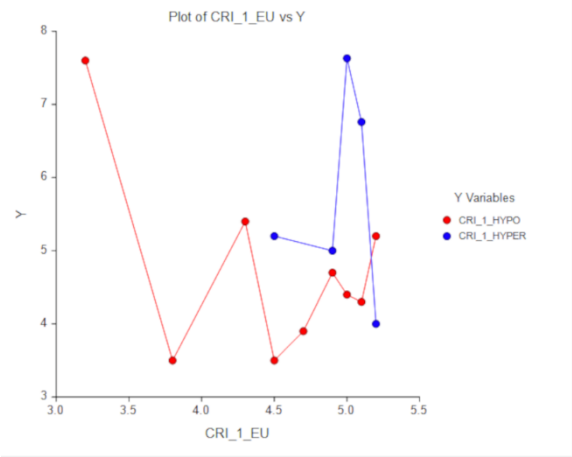

Figure 2: AUC-CRI-1 Y-axis (euthyroid) cases , X-axis hypo/hyperthyroid cases.

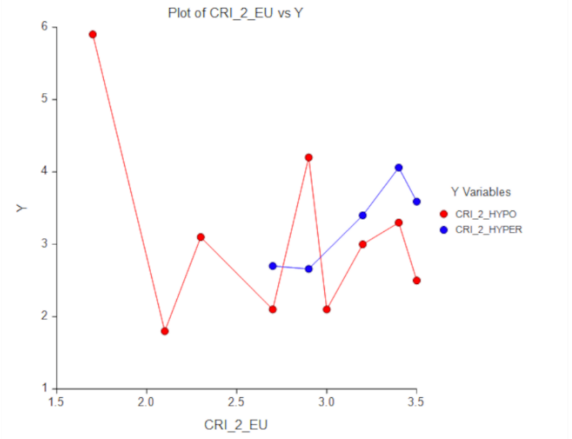

Figure 3: AUC-CRI-2 Y-axis (euthyroid) cases , X-axis hypo/hyperthyroid cases.

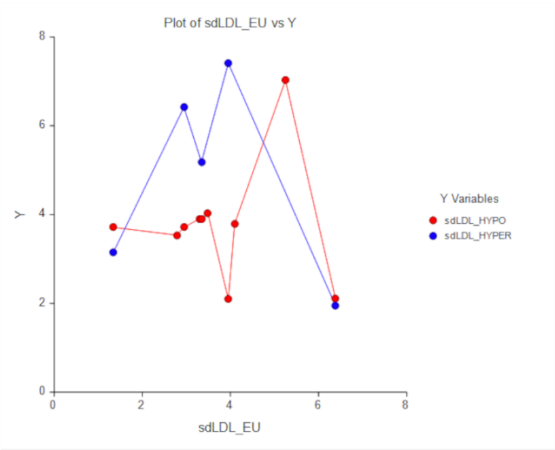

Figure 4: AUC-sdLDL Y-axis (euthyroid) cases , X-axis hypo/hyperthyroid cases.

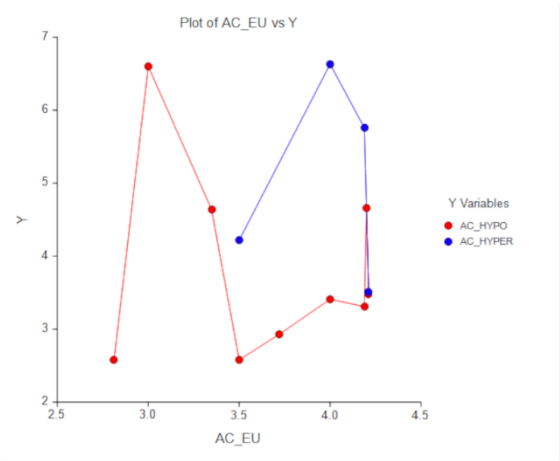

Figure 5: AUC-AC- Y-axis (euthyroid) cases , X-axis hypo/hyperthyroid cases.

Table 1: Mean and SD of biochemical parameters (N=number of cases).

Biochemical parameters	Hypothyroid cases	Hyperthyroid cases	Euthyroid cases
M (N)	15	5	15
F (N)	30	23	62
BMI (>30)	38.4±4.48	33.9±6.3	36.8 ± 4.47
T3(0.87-1.78mg/ml)	10.9 ± 30.89	22.87±39.6	1.33±1.84
T4(4.82-15.65mg/dl)	7.8±1.92	10.92±3.25	8.61±1.89
TSH(0.4-5.6IU/dl)	10.8±4.7	0.4±0.15	2.03±0.59
TG(>150mgs/dl)	139.4±46.08	183.8±94.47	168.15±48.26
TC(>200mgs/dl)	173.9±33.07	214.8±36.02	184.07±31.21
HDL(35-55mgs/dl)	37.2±4.84	38.2±4.66	39.4±5.44
LDL(>130mgs/dl)	112.2±38.32	123.8±13.3	112.2±29.74
AIP	0.21±0.12	0.31±0.19	0.24±0.12
CRI-1	4.7±1.22	5.72±1.45	4.71±1.17
CRI-2	3.1±1.25	3.28±0.59	2.91±0.77
sdLDL	3.78±1.35	4.82 ±2.25	4.26±1.77
AC	3.77±1.24	4.73±1.44	3.74±0.91

Table 2: ANOVA of mean±SD of T3, T4 and TSH with TG, TC, HDL and LDL in hypothyroid cases (N=45).

	With TG,TC,HDL and LDL			WITH Lipid ratios		
	F	**P**	**Sig.**	**F**	**P**	**Sig**
T3	43.951	<0.00001	+++	44.648	<0.00001	+++
T4	54.893	<0.00001	+++	28.301	<0.00001	++++
TSH	53.2388	<0.00001	+++	0.8162	0.521	NS

Table 3: ANOVA of Mean ±SD of TSH and TG, TC, HDL and LDL IN hypothyroid (45) and hyperthyroid (28) cases and euthyroid cases (77).

	Hypo vs hyper thyroid cases		Hyper vs euthyroid cases		Hypo vs euthyroid cases	
	F	**P**	**F**	**P**	**F**	**P**
TG	26.563	<0.00001	94.397	<0.00001	133 . 373	<0.00001
TC	141.85	<0.00001	369.512	<0.00001	382.660	<0.00001
HDL	125.189	<0.00001	170.449	<0.00001	441.664	<0.00001
LDL	327	<0.00001	518.814	<0.00001	148.732	<0.00001

The result is significant at p<.05

Table 4: Spearman's Rho correlation.

Euthyroid cases					
	AIP	**CRI-1**	**CRI-2**	**sdLDL**	**AC**
TSH rs	0.211	0.170	0.127	0.013	0.133
p(2-tailed)	0.288	0.394	0.527	0.946	0.507
T3 rs	0.098	0.257	0.335	0.082	0.223
p(2-tailed)	0.626	0.195	0.068	0.684	0.261
T4 rs	0.339	0.402	0.484	0.289	0.405
p(2-tailed)	0.082	0.037	0.010	0.142	0.035
Hyperthyroid cases					
TSH- rs	0.447	0.223	0.447	0.447	0.223
p(2-tailed)	0.450	0.717	0.450	0.450	0.717
T3 rs	0.4	0.1	0.5	0.4	0.1
p(2-tailed)	0.504	0.927	0.371	0.504	0.872
T4 rs	0.615	0.051	0.051	0.615	0.051
p(2-tailed)	0.269	0.934	0.934	0.269	0.934
Hypothyroid cases					
TSH- rs	0.079	0.115	0.188	0.115	0.006
p(2-tailed)	0.828	0.750	0.602	0.749	0.986
T3 rs	0.273	0.091	0.109	0.280	0.091
p(2-tailed)	0.444	0.802	0.763	0.432	0.802
T4 rs	0.042	0.273	0.340	0.024	0.212
p(2-tailed)	0.907	0.444	0.335	0.946	0.555

Negative correlation observed in all 3 groups r≤1.0; where the value r = 1 means a perfect positive correlation and the value r = -1 means a perfect negative correlation

Table 5: Multiple regression analysis with TSH as dependent variable.

	AIP		**CRI-1**		**CRI-2**		**sdLDL**		**AC**	
	SE	**P**	**SE**	**P**	**SE**	**P**	**SE**	**P**	**SE**	**P**
EUT	2.65	0.25	0.57	0.25	1.56	0.95	0.001	0.01	0.09	0.23
Hypo	2.75	0.34	0.31	0.18	0.31	0.66	0.002	0.007	0.03	0.02
Hyper	1.12	0.20	0.06	0.37	0.92	0.76	0.0006	0.01	0.17	0.08

DISCUSSION

Cardiovascular disease is leading cause of death in developing countries. Dyslipidemia was a proven risk factor. Situations leading to dyslipidemia include diabetes mellitus, metabolic syndrome, thyroid disorders and obesity. Reduced HDL, elevated triglycerides, LDL and TC aggravate atherosclerosis.[14] Thyroid dysfunction adversely effects lipid profile.[17] Lipid ratios indicate risk of atherosclerosis when the individual biochemical values are virtually within normal limits. In the present study the same findings were observed in all 3 groups irrespective of the thyroid status though the individuals have a BMI>30kg/m^2 (Table 1). Whereas lipid ratios were surely on higher range in all 3 groups. LDL/HDL ratio was <3.0 in Hyperthyroid subjects (2.91±0.77) whereas in hypothyroid and euthyroid subjects it was >3.0 (3.28±0.59 and 3.31±1.25 respectively). One way analysis of variance showed elevated lipid parameters and ratios in hypothyroid obese individuals (p value<0.00001) Table 2 and Table 4. This finding is consistent with that of James et al.[18] Individual biochemical values of lipoproteins correlated significantly positively with TSH between hyperthyroid-Hypothyroid; hyperthyroid-euthyroid and hypothyroid - eurthyroidobese individuals (Table 3) p value<0.00001. T3, T4 and TSH correlated negatively with lipid ratios in Spearman's Rho correlation analysis (Table 4) as well as in multiple regression analysis (Table 5) except sdLDL (TG/HDL-C) that showed significant correlation with TSH in all 3 groups (p value<0.01, <0.007 and <0.01). It was suggested by Dobiasova et al that high TG and low HDL-C concentrations induce a surge in sdLDL. The finding was consistent with that of Marwaha et al who suggested that TSH levels of >10IU/L were associated with higher TG, LDL-C and low HDL-C concentrations.[19] Further, Cerbone et al suggested increased TG/HDL-C ratio aggravates atherogenic risk and helps in identifying subjects with cardiovascular disease.[20] Similarly Subramanian et al suggested that small dense LDL are more susceptible to oxidation, partly due to less free cholesterol content.[21] sdLDL were relatively slowly metabolised which enhances their atherogenecity.[22]

CONCLUSION

Typical dyslipidemia of obesity includes increased TGs, decreased HDL-C and slightly elevated LDL-C and small, dense LDL. Thyroid disorders and obesity are prevalent in South India. Preventable vascular complications could be predicted much in advance using different lipid ratios rather than direct biochemical parameters. Non-HDL fraction (TC-HDL-C) was suggested as a surrogate marker for sdLDL as simple inexpensive method of predicting atherosclerosis. The study could be done for a longer period with clinical follow-up using Electrocardio graph, 2DEcho studies and patient outcome.

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