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HYPOTHYROIDISM AMONG PATIENTS WITH AND WITHOUT METABOLIC SYNDROME IN KERALA

Dr. Jayapal T.[1], Kamalu S.[2] and Rajasekharan C.[3]

[1]Assistant Professor of Medicine, Department of Medicine, Medical College Hospital, Thiruvananthapuram-695011.
[2]Senior Resident, Department of Medicine, Medical College Hospital, Thiruvananthapuram-695011.
[3]Professor of Medicine, Department of Medicine, Medical College Hospital, Thiruvananthapuram-695011.

*Corresponding Author: Dr. Jayapal T.

Assistant Professor of Medicine, Department of Medicine, Medical College Hospital, Thiruvananthapuram-695011.

ABSTRACT

Objective: The primary objective was to study the proportion of primary hypothyroidism among patients with and without metabolic syndrome. The secondary objective was to study the correlation between thyroid hormones T3, T4, TSH levels and metabolic syndrome parameters in the study group. **Methods**: A cross sectional study was conducted in a tertiary care centre in Kerala, South India. One hundred and eighty patients, between 18 to 55 years of age, with metabolic syndrome (NCEP ATP-3 criteria) were included in the study group. One hundred and eighty approximately age and sex matched controls, having no features of metabolic syndrome (0 out of 5 of ATP-3 criteria) were compared with the study group. Analysis of data was done using SPSS 11.0 version software. **Results**: The percentage of hypothyroidism among the control group is 10% while that of cases is 48%, which represents a statistically significant result {p <0.001}. Among the study group, the prevalence of subclinical hypothyroidism in males with metabolic syndrome is 11.7% and in females 26.2%. The prevalence of overt hypothyroidism in males with metabolic syndrome in the study group is 3.9% and in females with metabolic syndrome is 8.7% in the study group.T3 T4 and TSH levels showed varying correlation with components of metabolic syndrome. **Conclusions:** The prevalence of primary hypothyroidism is higher in patients with metabolic syndrome than it is in the control group. Subclinical hypothyroidism is more prevalent than overt hypothyroidism in patients with metabolic syndrome compared to the control group**.** The prevalence of hypothyroidism is higher in females with metabolic syndrome than it is in the control group. Sub-clinical hypothyroidism is more prevalent than overt hypothyroidism in both groups.

KEYWORDS: Overt Hypothyroidism, Metabolic syndrome, sub-clinical hypothyroidism, hypertension, dyslipidemia.

INTRODUCTION

Metabolic syndrome constitutes a cluster of risk factors characterized by hypertension, dyslipidemia, hyperglycemia, prothrombotic and proinflammatory conditions.[1] Its presence is a major risk for development of type 2 diabetes mellitus[2] and atherosclerosis.[3] Insulin resistance is the central pathophysiological process in metabolic syndrome.[4] Subclinical hypothyroidism and overt hypothyroidism are recognized risk factors for atherosclerotic cardiovascular disease, hyperlipidemia, low grade inflammation and hypercoagulability.[5,6,7] Some studies have shown that the prevalence of hypothyroidism is higher in patients with metabolic syndrome,[8,9] while others exhibit no association.[10,11] As metabolic syndrome and hypothyroidism are independent risk factors for the same disease process, namely, cardiovascular disease, it is possible that patients suffering from both these disease entities may have a compounded risk. Our study is an

effort to compare the proportion of primary hypothyroidism in patients with and without metabolic syndrome and assess the correlation between thyroid hormone levels and metabolic syndrome parameters.

METHODS

A cross sectional study was conducted in a tertiary care centre in Kerala, South India. One hundred and eighty patients, between 18 to 55 years of age, with metabolic syndrome (NCEP ATP-3 criteria) were included in the study group. In addition, approximately 180 age and sex matched controls, having no features of metabolic syndrome (0 out of 5 of ATP-3 criteria) were compared with the study group. The study continued for a period of three months. Patients with any known thyroid disorders, patients receiving any medications that alter thyroid functions or lipid levels, with cardiac failure, chronic liver disease, nephrotic syndrome, hepatic and renal

failure, with acute psychiatric problems and pregnant women were excluded.

Definition of Metabolic Syndrome
* Presence of metabolic syndrome in each patient was analysed as per the ATP III guidelines (with modifications for waist circumference recommended for South Asians).[19]
* Blood pressure (>130 systolic / >85 diastolic mmHg) or on anti-hypertensives.
* Plasma glucose (>fasting 110mg/dl) or on anti-diabetic medications.
* Triglycerides (>150mg/dl)
* HDL cholesterol (<40 mg/dl men; <50mg/dl women)
* Waist circumference (>90 cm men; >80cm women)
* The presence of three out of five of the above criteria is diagnostic of metabolic syndrome.

Thyroid hormone levels were assessed in both groups. Demographic data were collected from both the study and the control group baseline and a detailed physical examination was performed. The blood pressure [in mm of Hg] was recorded in the right arm, in the sitting position, with a mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 20 minutes apart and the mean of the two was taken. Waist circumference [in centimetres] was measured with the tape in the horizontal position, just above the iliac crest, at the end of normal expiration, with the subject standing erect and looking straight forward and the investigator sitting in front of the subject.

Fasting blood samples were obtained (venous blood samples taken after overnight fast of a minimum of 8 hrs); fasting blood sugar was tested in the Biochemistry Laboratory of Government Medical College using Glucose Oxidation method and Fasting Lipid Profile was tested in the ICMR Laboratory of Government Medical College Hospital using AT112 ACCUREX semi-auto analyzer. Serum TSH T3 and T4 measurements were taken using micro plate enzyme immune assay method. Typical adult reference ranges taken were serum TSH - 0.3 to 4.0 mU/L; serum total T4 - 5 to 12 μg/dL (65 to 155 nmol/L); serum total T3- 65 to 170 ng/dL (1.0 to 2.6 nmol/L).[17] A serum TSH level higher than the normal reference range and normal T3 and T4 levels were diagnosed as subclinical hypothyroidism (SCH). Patients with TSH levels above the reference range and T4 levels below the normal reference range were classified as being overt hypothyroid. Primary hypothyroidism included both overt and subclinical hypothyroidism. Patients with normal TSH and T4 levels were considered euthyroid.

Statistics
Base line characteristics of the study participants were expressed as mean+/-2SD and as a percentage. Chi-square test and Fischer's Exact Test were used for comparison of qualitative variables in case and controls. Intergroup comparisons of quantitative variables was analysed by independent sample t -test. A p value <0.05 was considered significant. Pearson's correlation co-efficient was used to assess the correlation between T3, T4, TSH and metabolic syndrome parameters. Analysis was carried out using SPSS 11.0 version.

RESULTS

The mean age of controls was 39.9 ± 9.2 and mean age of cases were 40.6 ± 6.9 (p>0.05). The control group consisted of 84 [46.7%] males and 96 [53.3%] females. Among the cases 77 [42.8%] were males and103 [57.2%] were females.

Of the control group, 162 [90%] patients were euthyroid and 14 [7.8%] were subclinical hypothyroid and 4[2.2%] were overt hypothyroid. Of the cases, 132 [73.3%] patients were euthyroid, 36 [20%] were subclinical hypothyroid, and 12 [6.7%] were overt hypothyroid [Table.1].

Table 1: Comparison of thyroid status based on category.

Thyroid status	Control		Case		χ^2	p
	Count	Percent	Count	Percent		
Euthyroid	162	90.0	132	73.3		
Subclinical hypothyroid	14	7.8	36	20.0		
Overt hypothyroid	4	2.2	12	6.7	16.74**	0.000
T3	101.5 ± 29		94.8 ± 21.6			
T4	9.5 ± 11.5		8.4 ± 3.8			
TSH	4.8 ± 15.7		6.6 ± 13.6			

**: - Significant at 0.01 level

It can thus be seen that the number of patients with subclinical hypothyroidism and overt hypothyroidism is higher among the cases, and the difference is statistically significant (p = 0.00). The percentage of hypothyroidism among the control group is 10% and among the cases is 48% (p<0.001)[figure. 1].
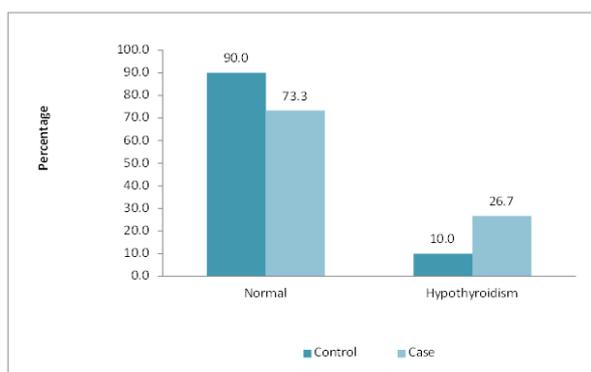
Figure 1: Comparison of thyroid status based on category.

The prevalence of subclinical hypothyroidism in males with metabolic syndrome is 11.7% and in females 26.2%.[figure.2].
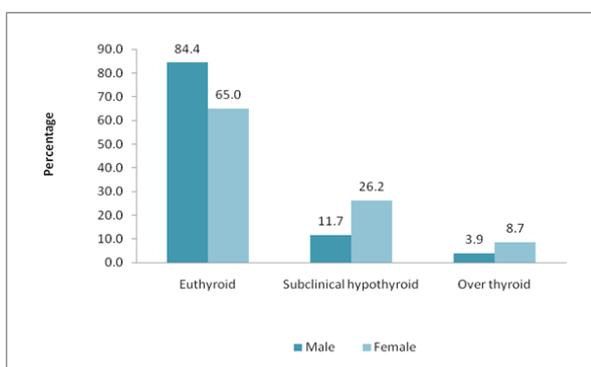

Figure 2: Association between thyroid status and sex among metabolic syndrome.

The prevalence of overt hypothyroidism in males with metabolic syndrome is 3.9% and in females 8.7% (p = 0.015).

T3 showed a significant negative correlation with systolic blood pressure in patients with metabolic syndrome [Table. 2].

Comparison of thyroid status based on Category among patients with metabolic syndrome

Table. 2. Pearson correlation between thyroid hormones as measured by T3, T4, TSH levels and metabolic syndrome parameters among those having metabolic syndrome

Parameters	T3		T4		TSH	
	r	p	r	p	r	p
FBS	-0.115	0.126	-0.035	0.639	0.062	0.406
SBP	-0.2**	0.007	-0.098	0.188	0.142	0.057
DBP	-0.121	0.105	0.003	0.966	0.067	0.373
TC	-0.096	0.201	-0.094	0.212	0.063	0.401
HDL	0.035	0.640	0.164*	0.028	-0.139	0.062
LDL	-0.023	0.764	-0.051	0.498	0.01	0.895
TG	0.021	0.776	-0.027	0.719	0.029	0.700
WC	-0.127	0.090	0.118	0.026	0.24**	0.001

*: - Significant at 0.05 level **: - Significant at 0.01 level

T3 showed a significant negative correlation with waist circumference in patients with hypothyroidism and metabolic syndrome [table. 3].

Comparison of thyroid status based on Category among patients with metabolic syndrome and hypothyroidism

Table. 3. Pearson correlation between thyroid hormones by T3, T4, TSH levels and metabolic syndrome parameters among those having metabolic syndrome and hypothyroidism

Parameters	T3		T4		TSH	
	r	p	r	p	r	p
FBS	-0.136	0.357	-0.009	0.954	0.186	0.206
SBP	-0.127	0.390	-0.154	0.295	0.095	0.519
DBP	-0.199	0.176	-0.007	0.963	0.23	0.116
TC	-0.002	0.992	-0.04	0.789	0.057	0.699
HDL	0.125	0.399	0.357*	0.013	-0.043	0.769
LDL	-0.036	0.809	-0.021	0.889	0.1	0.499
TG	-0.225	0.123	-0.04	0.785	0.139	0.348
WC	-0.4**	0.005	-0.317*	0.028	0.247	0.090

T3 showed a significant negative correlation with diastolic BP in patients who are euthyroid and with metabolic syndrome [table. 4].

Comparison of thyroid status based on Category among patients with metabolic syndrome and euthyroidism

Table 4: Pearson correlation between thyroid hormones as measured by T3, T4, TSH levels and metabolic syndrome parameters among those having metabolic syndrome and are euthyroid

Parameters	T3		T4		TSH	
	r	p	r	p	r	p
FBS	-0.069	0.429	0.016	0.853	0.038	0.666
SBP	-0.137	0.116	-0.017	0.845	0.089	0.310
DBP	-0.216*	0.013	-0.079	0.369	0.122	0.163
TC	-0.038	0.662	-0.144	0.099	0.068	0.441
HDL	-0.107	0.220	0.053	0.544	-0.02	0.822
LDL	0.064	0.467	-0.131	0.133	-0.035	0.694
TG	0.046	0.600	-0.058	0.506	0.091	0.300
WC	0.2*	0.021	0.198*	0.023	-0.188*	0.031

*: - Significant at 0.05 level **: - Significant at 0.01 level

DISCUSSION

Among the 180 controls, prevalence of hypothyroidism was 10%. Among the 180 cases, prevalence of hypothyroidism was 26.7%(p<0.001). Among the 180 controls, 162 (90%) patients were euthyroid, 14 (7.8%) were subclinical hypothyroid, and 4 (2.2%) were overt hypothyroid. Among the180 cases, 132 (73.3%) were euthyroid, 36 (20%) were sub clinically hypothyroid and 12 (6.7%) were overt hypothyroid. Thus, the prevalence of hypo-

thyroidism is higher in patients with metabolic syndrome compared to the control group. Among the patients with hypothyroidism, subclinical hypothyroidism was more prevalent than overt hypothyroidism. The prevalence of subclinical hypothyroidism in males with metabolic syndrome is 11.7% and in females is 26.2%. The prevalence of overt hypothyroidism in males with metabolic syndrome is 3.9% and females 8.7%.These differences obtained in both groups, and were statistically significant (p = 0.00). Thus, the prevalence of hypothyroidism is higher among females in both the case and control groups. Subclinical hypothyroidism was more prevalent than overt hypothyroidism in females. Uzunlulu et al. [8] conducted a study to assess the prevalence of subclinical hypothyroidism in patients with and without metabolic syndrome and it was found in 36 (16.4%) cases in the metabolic syndrome group and in 11 (5.8%) cases in the control group (p = 0.001). Prevalence of SCH was higher in females with metabolic syndrome than it was in the control (p = 0.0001). It was similar in both groups of male patients.The study also found higher blood pressure, LDL cholesterol and triglyceride levels and lower HDL cholesterol levels among metabolic syndrome patients compared to controls. No association could be demonstrated between these parameters and SCH, but they do suggest a need for investigating the presence of SCH during the management of metabolic syndrome patients.Another study by Ghanshyam Palamaner et al.[9] looked into the association between primary hypothyroidism and metabolic syndrome in a cross sectional study in Chennai, using 420 patients with metabolic syndrome and 406 controls. Of the 420 patients in the study group, 240 were females and 180 were males, with a mean age of 51 ± 9.4 years. Of the 406 patients in the control group, 216 were females and 190 males with mean age 49 ± 11.2 years.In the study group, 92 had subclinical hypothyroidism (SCH) (21.9%), 31 were overtly hypothyroid (7.4%) and 297 were euthyroid (70.7%). In the control group, 27 patients had subclinical hypothyroidism (6.6%), 9 patients had overt hypothyroidism (2.2%) and 370 patients were euthyroid (91.2%). On comparison subclinical hypothyroidism (P < 0.001) and overt hypothyroidism (P < 0.001) were significantly associated with the study group as compared to the control group. Logistical regression analysis indicated an association between female gender (P = 0.021) and subclinical hypothyroidism and female gender (P = 0.01) and overt hypothyroidism in the study group. Thus, hypothyroidism is associated with metabolic syndrome and females are more at risk.

The secondary objective of our study was to assess the correlation between T3, T4 and TSH levels and metabolic syndrome parameters. Among the cases, correlation was found in all patients and separately in hypothyroid and euthyroid patients.In our study, T3 showed a significant negative correlation with systolic blood pressure in patients with metabolic syndrome. T3 showed a significant negative correlation with waist circumference in patients with hypothyroidism and metabolic syndrome.

T3 showed a significant negative correlation with diastolic BP in patients who are euthyroid and with metabolic syndrome. Most of the studies used FT3 and FT4 assays and were conducted with euthyroid groups. The results of the various studies conducted in different parts of the world regarding the correlation between T3, T4 and TSH levels and parameters of metabolic syndrome yielded inconclusive results. Some of the salient features of these studies are described below.Shih-Yi Lin et al.[12] conducted a study in a Chinese population that showed that the serum free thyroxine concentrations showed a statistically significant correlation with triglyceride and body mass index, respectively (P < .01), but not with blood pressure, glucose level, or high-density lipoprotein cholesterol level in 220 cases and 190 controls sudied. Subclinical hypothyroidism[13] in their study of 45 Kuwaiti women found that total T3 showed a positive correlation with triglycerides, low density lipoprotein- cholesterol (LDL-C), total cholesterol, and insulin, and negatively with body fat. Thyroid-stimulating hormone correlated positively with BMI, insulin, LDL-C and negatively with HDL-cholesterol (P<0.05). Free triiodothyronine correlated positively with waist circumference and T4 did not correlate with metabolic syndrome parameters.

G. De Pergola et al.[14] showed FT3 was directly associated with BMI (P<0.01) and waist circumference (*P*<0·01), and negatively correlated with age (P<0.001). FT4 was negatively associated with HOMA-IR (*P* <0·05) and fasting insulin levels (P<0.05). TSH was positively correlated with waist circumference (*P*<0·05) and negatively associated with age (P<0.05). Beom-Jun Kim et al.[15] in a study of euthyroid obese subjects showed that, in males, serum FT4 concentrations were positively associated with BP, fasting glucose, HDL-C, and TG levels, and negatively associated with waist circumference after adjustment for age (P for trend = 0.033 to < 0.001). Females also showed similar findings except that FT4 had no correlation with TG after adjustment for age (all P< 0.001 except TG). The negative association between FT4 and waist circumference was not present in younger male subjects (< 50 years), and the positive association between FT4 and BP was more prominent in younger female subjects (< 50 years) than in older females (P <0.05). Hyun Tae Park et al.[16] conducted a study to investigate the relationship between thyroid stimulating hormone (TSH) and metabolic syndrome in euthyroid postmenopausal women in a cross sectional study of 2205 Korean post-menopausal women. They found out that TSH levels were associated with total cholesterol, LDL-cholesterol, triglycerides and diastolic blood pressure. Using a multiple linear regression analysis, LDL-cholesterol, and triglycerides levels were identified as independently associated with TSH. Multivariate logistical regression analysis determined that TSH levels strongly contributed to metabolic syndrome. Ghanshyam et al.[9] in their study of subjects with metabolic syndrome showed that thyroid function is consistently associated with individual components of metabolic syndrome. The association with serum lipids was line-

ar across the entire reference range of TSH. With regard to other components of metabolic syndrome, a low normal FT4 level was significantly associated with increased insulin resistance, and subclinical hypothyroidism has been associated with fasting hyperinsulinemia. Diastolic arterial pressure has been significantly associated with TSH levels and T4 resistance-index (freeT4, TSH product). Since these studies have yielded contradicting results, a large scale study is required in our population taking into consideration the environmental, ethnic and geographical characteristics influencing the variables.

CONCLUSIONS

The prevalence of primary hypothyroidism is higher in patients with metabolic syndrome than it is in the control group. Subclinical hypothyroidism is more prevalent than overt hypothyroidism in patients with metabolic syndrome than it is in the control group. Hypothyroidism is more prevalent in females with metabolic syndrome than it is in the control group. Subclinical hypothyroidism is more prevalent than overt hypothyroidism in both groups. Patients with metabolic syndrome may be screened for thyroid abnormalities for early detection of thyroid disorders and early intervention so as to reduce the added cardio-vascular risk of thyroid abnormalities.

FUTURE WORK

The author suggests an early screening for thyroid dysfunction in patients with metabolic syndrome, the rationale for this being that an early intervention aiming at a euthyroid state will significantly reduce the cumulative cardiovascular morbidity and mortality. As the results of the studies conducted in different parts of the world regarding the correlation between T3, T4, TSH and parameters of metabolic syndrome yielded inconclusive results, a large scale study is necessary, taking into consideration the environmental, ethnic and geographical characteristics influencing the variables. It is also suggested to develop guidelines in our population in patients with metabolic syndrome regarding the level of TSH at which subclinical hypothyroidism is to be treated.

Author contribution
This work was carried out in collaboration between all authors. Authors TJ, KS and CR were responsible for conception of the idea and conducting the study. All the authors' were responsible for writing, re-writing, editing and formatting of the manuscript, tables and figures and referencing. Authors TJ and CR were responsible for revising the manuscript. All authors read and approved the manuscript.

Consent: All authors declare that 'written informed consent was obtained from the patients (or other approved parties) for collecting the data and participating in this study.

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