Assessment of Thyroid Dysfunction in Patients with Metabolic Syndrome and its Correlation with Individual Parameters of Metabolic Syndrome

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ABSTRACT

Introduction: Metabolic syndrome is increasing rapidly all over the world. There has been an increasing amount of evidence to suggest that metabolic syndrome is associated with many endocrine disorders, including thyroid disorders. The presence of thyroid disorders in patients with metabolic syndrome may increase the risk of cardiovascular disease. This study was carried out to evaluate for thyroid disorders in patients with metabolic syndrome and to assess its connection with individual parameters of metabolic syndrome.

Material and methods: A prospective observational study was done for a period of 20 months in our tertiary care hospital. All the patients fulfilling the International Diabetes Federation criteria for metabolic syndrome were enrolled. Sociodemographic data, anthropometric measurements, blood pressure, were recorded. Blood samples were analyzed for glucose, triglycerides, high-density lipoprotein, cholesterol, and thyroid hormones (Thyroid-stimulating hormone and Thyroxine) in fasting state.

Results: Among 92 patients studied, thyroid dysfunction was noted in 18.47% (n=17). Subclinical hypothyroidism (14.13%, n=13) was the most common thyroid dysfunction noted. Overt hypothyroidism was found in 4.34% (n=4) of subjects. The prevalence of thyroid dysfunction was more in females (15.21%, n=14) compared to male patients, which was statistically significant (p=0.007). The association of thyroid dysfunction with each parameter of metabolic syndrome was not statistically significant.

Conclusion: Thyroid dysfunction is common among patients with metabolic syndrome. A higher prevalence of subclinical hypothyroidism, especially among female patients with metabolic syndrome, emphasizes the need for careful evaluation of thyroid disorders in patients with metabolic syndrome.

Keywords: Metabolic Syndrome, Thyroid, Hypothyroidism, Thyrotropin, Triglycerides

INTRODUCTION

The prevalence of Metabolic Syndrome (MS) is on raise all over the world, including India and other South Asian countries.[1] MS is characterized by hypertension, dyslipidemia, hyperglycemia, and prothrombotic and pro-inflammatory conditions, which accelerate the risk for the atherogenic process in the body. The MS is also known as syndrome X, the insulin resistance syndrome, and the deadly quartet.[1,2,3] The constellation of metabolic abnormalities includes impaired glucose intolerance, insulin resistance, central obesity, lipid abnormalities, and hypertension, as well-known risk factors for cardiovascular disease. When grouped, they are associated with more risk of cardiovascular disease.[4,5,6] Klein, a Swedish physician, first described MS in 1920 as the clustering of hypertension, hyperglycemia, and gout.[7] Hypothyroidism is well known to cause hyperlipidemia, raised diastolic blood pressure, endothelial dysfunction, and cardiovascular disease. Insulin resistance is the main culprit in the occurrence of MS. According to recent studies, insulin resistance also leads to dyslipidemia in hypothyroidism. As the risk of cardiovascular catastrophes increase with MS and hypothyroidism, there is a definite need to identify the hypothyroid status in MS patients. This study was carried out to evaluate for thyroid disorders in patients with metabolic syndrome and to assess its connection with individual parameters of metabolic syndrome.

MATERIAL AND METHODS

This was a prospective observational study done for 20 months from January 2018 to August 2019 among the outpatients and inpatients of PES institute of medical sciences and research, Kuppam.

Inclusion criteria

Adult patients who fulfill the new International Diabetes Federation (IDF) criteria of MS were enrolled.

Exclusion criteria

Persons < 18 years of age.
Patients with liver disorders,
Patients with renal disorders and congestive cardiac failure
Acutely ill patients
Pregnant women
Patients under treatment for any other thyroid-related disease
Subjects who were not willing to enroll in the study

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Sample size: As per the formula, the sample size was calculated to be 92.
Sample size = Z^2 x p x (1-p) / c^2
Where:
Z = Z value (e.g. 1.96 for 95% confidence level)
p = percentage picking a choice, expressed as decimal
(0.5 used for sample size needed)
c = confidence interval, expressed as decimal
(e.g., .04 = ±4)

Procedure for data collection

This study was conducted among inpatients and outpatients of the Department of Medicine, PES hospital, Kuppam. Patients with features suggestive of MS according to the new International Diabetes Federation (IDF) criteria were assessed for thyroid dysfunction after taking written informed consent in their vernacular language. Before starting the study, Institutional ethics committee approval was obtained. Early morning fasting blood sample was taken to estimate serum thyroid-stimulating hormone (TSH) and free thyroxine FT4. All the demographic data (age, gender, education, weight, height), body mass index (BMI), socioeconomic status, occupation, waist circumference (WC), blood pressure, fasting plasma glucose (FPG), triglycerides (TG), and high-density lipoprotein (HDL) of these MS patients documented.

New International diabetes federation (IDF) criteria[8]

According to the new IDF definition, for a person defined as having the MS they must have:
central obesity (defined as waist circumference with >90 cms in males and ≥80 cms in females)
and any two of the following four factors:

1. Raised triglycerides - ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
2. Reduced HDL cholesterol - < 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
3. Raised blood pressure - SBP ≥ 130 or DBP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
4. Raised fasting plasma glucose - (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

If BMI is >30kg/m2, central obesity can be assumed, and waist circumference does not need to be measured.

The reference range for TSH was 0.25–5.5 µIU/ml, and for FT4 9–24 pmol/L. A high serum TSH level up to 10 µIU/ml with FT4 levels within the reference range was considered as subclinical hypothyroidism. Patients with high TSH of >10 µIU/ml with low/normal FT4 levels classified as being overtly hypothyroid. Patients with normal TSH and FT4 were considered euthyroid. In patients who were diagnosed as hypothyroidism was followed and treated according to standard practice guidelines. A chi-square test was applied to the collected data to draw scientific conclusions using software SPSS 22.

RESULTS

A total of 92 subjects were included in this study based on the inclusion and exclusion criteria of MS. Among them, 49 were women, and 43 were men. Age of the women ranged from 36 to 78 years with mean age 45.1 years and Standard Deviation 7.6. In this study, the age of male patients ranged from a minimum of 38 to a maximum of 82 years, with a mean of 46.5 years and a standard deviation of 9.7. The majority of the patients were in the age group of 61-70 years. (40.2%, n=37)

In this study population, 23 patients fulfilled three parameters of MS, 47 patients fulfilled four parameters required for MS. All parameters of MS were found in 22 patients. (table 1) The mean height of the study population was 161.75 cms, and mean WC was 95.64 cms. The mean BMI of the subjects was 32.47, and the standard deviation was 2.94. In this study, all the patients had WC>90 cms in men and >80 cms in females. The mean and standard deviation of WC in our study was 95.64 ± 6.61. In this study, impaired glucose tolerance was seen in 88 subjects. Hypertension was seen in 76 (82.6%) out of 92 patients. In this study, raised TGL was seen in (65.21%) 60 patients. The mean and standard deviation was 171.6 mg/dl and 58.54. HDL-C reduced in 51 (55.43%) patients. In this study, HDL-C mean and standard deviation was found to be 44.44 mg/dl and 7.59. All the variables used for MS parameters were depicted in table 2.

The TSH in this study ranged from 0.55 µIU/L to 33.73 µIU/L, and free T4 levels ranged from 8.02 ng/dl to 23.3 ng/dl. Patients in this study, were categorized into 4 groups according to the definitions based on TSH and FT4 levels. According to our definitions, 81.52% (n=75) patients found to be euthyroid. Thyroid abnormalities were detected in 18.47% (n=17). Overt hypothyroidism was found in 4.13% (n=4) of patients. Subclinical hypothyroidism was found in 14.13% (n=4). There were no overt hyperthyroid or sub-clinical hyperthyroidism patients in this study. The prevalence of thyroid dysfunction in females was higher than males in MS patients, which was highly significant statistically. P-value was 0.007, and the chi-square statistic is 7.0898. The thyroid status of the study subjects according to age is depicted in table 3.

Based on the MS criteria, of those twenty-three patients who fulfilled three of the five risk factors two had thyroid dysfunction (2-hypothyroid); of the forty-eight patients who had four risk factors seven had thyroid dysfunction (3 hypothyroid and four subclinical hypothyroid); of the twenty-one patients who had all five risk factors, eight had thyroid dysfunction (1 overt hypothyroid and seven subclinical hypothyroid). (table 4) In this study, we have studied the association of each of the MS parameters with the thyroid dysfunction, which was depicted in table 5. Due to the smaller sample size, the association of thyroid dysfunction with each

Criteria for Metabolic Syndrome	Number	Percentage (%)
3 parameters	23	25.0
4 parameters	47	51.09
5 parameters	22	23.91
Total	92	100

Table-1: No of criteria positive for MS in subjects

Parameters	Minimum	Maximum	Mean	Standard Deviation
Age (years)	36	82	59.55	9.37
Height (cms)	148	180	161.75	6.07
Weight (kgs)	73	108	84.81	7.50
BMI	26.2	40.0	32.47	2.94
Waist Circumference (cms)	82	116	95.64	6.61
Systolic Blood Pressure (mm of HG)	100	180	140.7	15.26
Diastolic Blood Pressure (mm of HG)	62	110	88.95	8.88
Fasting Blood Sugar (mg/dl)	96	343	145.46	43.84
Total Cholesterol (mg/dl)	119	297	192.56	33.32
High Density Lipoprotein (mg/dl)	22	57	44.44	7.59
Triglycerides (mg/dl)	77	484	171.60	58.54
Free T4 (ng/ml)	8.02	23.3	14.17	2.80
Thyroid Stimulating Hormone (IU/ml)	0.55	33.73	3.92	5.43

Table-2: Descriptive statistics of the variables in study population

Group	No	%	Male n (%)	Female n (%)
Euthyroid	75	81.53%	40 (43.47)	35 (38.04)
Hypothyroid	4	4.34%	2 (2.1)	2 (2.1)
Subclinical Hypothyroid	13	14.13%	1 (1)	F
Subclinical Hyperthyroid	0	0%	0	0
Hyperthyroid	0	0%	0	0
Total	92	100%	43 (46.73)	49 (53.26)

Table-3: Thyroid status of the study population

Metabolic Syndrome criteria fulfilled	Euthyroid (%)	Hypothyroid (%)	Subclinical Hypothyroid (%)	Subclinical Hyperthyroid	Total (%)
3	21 (22.82)	0	2 (2.17)	0	23 (25)
4	37 (40.21)	3 (3.26)	4 (4.34)	0	48 (52.17)
5	17 (18.47)	1 (1.08)	7 (7.6)	0	21 (22.82)
Total	75 (81.52)	4 (4.34)	13 (14.13)	0	92 (100)

Table-4: Metabolic syndrome parameters wise thyroid dysfunction

Metabolic Syndrome parameters	Thyroid status	Number	Mean	Standard deviation	P value
Waist circumference					
> 90 cms/ ≥ 80 cms	Euthyroid	75	95.54	6.20	0.7749
	Thyroid dysfunction	17	96.05	8.38	
Systolic blood pressure ≥ 130 mm Hg	Euthyroid	75	141.44	15.18	0.3885
	Thyroid dysfunction	17	137.88	15.72	
Diastolic blood pressure ≥ 85 mm Hg	Euthyroid	75	89.04	8.97	0.8510
	Thyroid dysfunction	17	88.58	8.73	
Fasting blood glucose ≥ 100 mg/dl	Euthyroid	75	142.97	42.12	0.2540
	Thyroid dysfunction	17	156.47	50.68	
High density lipoprotein <40mg/dl	Euthyroid	75	44.73	6.75	0.4482
	Thyroid dysfunction	17	43.17	10.70	
Triglycerides ≥ 150 mg/dl	Euthyroid	75	169.34	51.48	0.4394
	Thyroid dysfunction	17	181.58	84.29	

Table-5: Distribution of MS parameters in Euthyroid and Thyroid dysfunction

of the MS parameters was not statistically significant in this study.

DISCUSSION

The prevalence of MS is highly age-dependent and differs with different diagnostic criteria. Females have a prevalence of MS than males all over the world. The prevalence has increased from 7% in patients aged 20-29 to 44% among those aged 60-69 years.[9] The prevalence of MS in the whole world varies widely from <10% to 84%, depending on the region, age & sex distribution, the ethnicity of the population studied, and the parameters used for assessment of MS.[10] In India, the prevalence of MS is increasing due to increasing urbanization, increased intake of junk foods, and

reduced physical activity. The prevalence of MS in South India, according to various studies, ranged from 22.1% to 41%.[11] The prevalence of thyroid dysfunction (5.9%) and hypothyroidism (4.6%) in MS patients is higher than the prevalence in the healthy population.[12]

In the present study majority, 40.2% of MS patients are in the age group of 61-70 years. In a study by Prasad et al., 65.6% of MS patients belonged to the age group of 60-69 years.[12] In an Italian study done by Mannucci et al., the prevalence of MS was 52.8% in people aged >60 years, which was higher than in the present study.[13] The prevalence of MS increased in the same age and gender from the 20th century to the 21st century. In a US-based study, the prevalence during 1988-94 was 25.3%, which increased to 34.2% in 2007-2012. In this study, the prevalence increased in non-Hispanic white men compared to non-Hispanic black men. In the same study non-Hispanic, black women had more prevalence than non-Hispanic white women. So, according to this study, MS varies between race/ethnicity and period of study.[14]

In this study, the prevalence of MS in males was 46.7% (n=43), and in females, it was 53.3% (n=49), indicating a female predominance. In a study done by Meher et al., the prevalence of MS was more in females than males (55% vs. 45%). The increased prevalence in females can be attributed to abdominal obesity, reduction in HDL-C after attaining menopause, hyperandrogenism, and insulin resistance.[15]

In the present study, the mean and standard deviation of BMI was (32.47+/-2.94). The majority of subjects in this study, 62% (n=57), fall in the category of class I obesity. According to an Indian study done by Saikat kanjilal, the mean and standard deviation of BMI was 26.97 ± 4.5, which was less compared to the present study.[16]

In this study, all the patients had WC>90 cms in men and >80 cms in females. In Deshmukh et al., research the mean and standard deviation was correlating with our study of 98.6 ± 9.70. Subcutaneous fat and visceral fat together constitute the total abdominal circumference. The cardiovascular risk is more in patients with more visceral fat than subcutaneous fat. So, for the same WC in different populations, the distribution of subcutaneous fat and visceral fat varies. For example, Asians and Indians had more visceral fat than subcutaneous fat. On the contrary African and Americans have more subcutaneous fat than visceral fat. So, for the same WC, Indians, and Asians had more risk of diabetes and cardiovascular events than Africans and Americans.[17]

In this study, raised TGL was seen in 65.2% of individuals. The mean and standard deviation were 171.6 mg/dl and 58.54. In a study done by Kota et al., the mean and standard deviation of TGL was 165.87 ± 19.53 mg/dl.[18] Hypertriglyceridemia stimulates the enzyme cholesterol ester transfer protein, which leads to the transfer of TGL from TG-rich lipoproteins to HDL and LDL in exchange for cholesteryl esters leading to an increase in TG content of HDL and LDL.[19] Insulin resistance gets preceded by visceral obesity and increased intra-abdominal fat.[20] Increasing insulin resistance is mainly involved in two events. Firstly, the visceral adipocyte becomes more sensitive to the lipolytic hormones glucocorticoids and catecholamines in insulin resistance.[21] This hormonal lipolytic activity produces an increased flux of free fatty acids into the portal system, which serves as a hepatic substrate to assemble TGLs and TGL rich VLDLs. Secondly, enhancing insulin resistance leads to increased production of Apo B, the major protein of LDL, and as a consequence of the increased synthesis and secretion of TGL containing VLDL cholesterol particles.[22]

HDL-C was reduced in 55.4% of our patients. In a study by Kota SK et al., a similar reduction in the level of HDL-C was found.[18]

In this study, 95.65% of MS patients had impaired glucose tolerance. In MS, insulin resistance leads to impaired suppression of glucose and reduced glucose uptake in insulin-sensitive tissues. This leads to increased secretion of insulin and maintain glucose. Eventually, all the compensatory mechanisms fail, and impaired glucose tolerance leads to diabetes mellitus.

In this present study, 82.6% of MS patients had raised blood pressure satisfying one of the components of MS. According to a study done by Meher et al., the mean systolic blood pressure was less compared to our present study. Even the mean diastolic blood pressure of Meher's study was less compared to our research.[15]

In this study, thyroid dysfunction was seen in 18.47% (n=17) of MS patients. Among these thyroid dysfunction patients, subclinical hypothyroidism was seen in 14.13%(n=13), and overt hypothyroidism was seen in 4.34% (n=4) among MS patients. There were no cases reported of either overt or subclinical hyperthyroidism in our study population. In a study by Deshmukh, 28% of MS patients were diagnosed to have thyroid dysfunction (overt and subclinical as 17.6% and 8.10%).[17] In other Indian studies done by Kota et al. and Shantha et al., the prevalence of hypothyroidism was 26% and 29.3%.[18,23] According to various studies done on patients with MS, there was a higher prevalence of subclinical hypothyroidism ranging from 14.6% to 53%, and overt hypothyroidism ranging from 3.5% to 7.4%.[24–26]

In this study, each parameter of MS was studied for the association with thyroid dysfunction, but due to a smaller sample size, the association was not found to be statistically significant. In a similar study done by Khatiwada, each component of MS was correlated with TSH and free T4, but only HDL was statistically significantly associated with TSH.[27]

In this study, 15.21% of women had thyroid dysfunction compared to men who had 3.26%. The prevalence of thyroid dysfunction in females was higher than males with MS patients, which was highly significant statistically. (p-value = 0.007) In many of the studies, women had a high prevalence of MS compared to men.[28-30] In this study, thyroid dysfunction was seen in 13.67% of subjects who were >50 years and only in 3.33% of MS patients <50 years of age. Deshmukh et al. found men and women >45 years had a higher incidence of thyroid dysfunction than those who were <45 years of age.[17] In these hypothyroidism patients, treatment with levothyroxine replacement reverses the symptoms and signs

of hypothyroidism, thereby those factors which mimic MS. Hypothyroidism are also associated with lipid abnormalities, impaired glucose tolerance, weight gain, and hypertension. Thus, hypothyroidism has features that mimic the characteristics of MS.[31,32] It is well known and proven that, by treating with levothyroxine replacement in all overt or clinical hypothyroid patients, we can reduce all the metabolic parameters and cardiovascular risk. Management of patients with subclinical hypothyroidism remains controversial because the body of scientific evidence available to guide clinical decisions is limited. The progression rate from subclinical hypothyroidism to overt hypothyroid is 2-5% per year.[33]

A meta-analysis report shows that levothyroxine therapy in individuals with subclinical hypothyroidism lowers mean serum total and LDL-C concentration significantly, and the reduction in serum cholesterol may be more massive in individuals with higher pre-treatment cholesterol levels.[34] As the MS patients have hyperlipidemia, diabetes, hypertension, and increased cardiovascular risk, it looks logical to treat MS patients having subclinical hypothyroidism by levothyroxine replacement therapy. This study shows that one-fifth of MS patients had hypothyroidism either overt or subclinical. This finding indicates a need for investigating the presence of thyroid dysfunction during managing MS patients.

Limitations

This study was a cross-sectional study, so cause to effect relations couldn't be assessed.

1. FT3 was not analyzed in our study.
2. Smaller sample size, so it is difficult to generalize the results to a larger population.

Recommendations of areas for future research

1. Interracial/ethnic differences and the interregional difference in the prevalence of MS and the association of MS parameters with thyroid disorders should be assessed.
2. Many studies were done on the gender and age-related association of MS and its parameters, but the occupational-related association was not executed in any of the studies. Future research related to the association of occupation and MS may be concentrated.

CONCLUSION

The prevalence of thyroid dysfunction in females is higher than in males with MS, which was highly significant statistically (P=0.007). Prevalence of Subclinical hypothyroidism and Hypothyroidism were 14.13% and 4.34% in MS patients, which was more than that of the general population. This study emphasizes the need for careful evaluation of thyroid disorders in patients with MS.

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