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CORRELATION OF THE LEVELS OF THYROID HORMONES WITH VARIOUS COMPONENTS OF METABOLIC SYNDROME IN PATIENTS DIAGNOSED WITH METABOLIC SYNDROME

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ABSTRACT

Background and Objectives: Metabolic syndrome (MetS) is a cluster of several metabolic disorders including hyperglycemia, reduced high density lipoprotein cholesterol, raised triglyceride level in serum, hypertension and abdominal obesity. Thyroid dysfunction (TD) was found to be more frequent between patients with metabolic syndrome. MetS and its related components are associated with functional and morphological alteration of the thyroid gland. **Methods:** The present study was conducted at the MM Institute of Medical Sciences and Research. The study includes 300 patients with MetS as a case and 300 healthy volunteers as a control. MetS was diagnosed according to international diabetes federation. Thyroid profile was assayed in various components of metabolic syndrome. **Results:** It was noted that thyroid dysfunction was prevalent in 129 patients out of 300 MetS patients included in our study. Out of which, 46 patients had hypothyroidism, 18 patients had hyperthyroidism, 58 patients had subclinical hypothyroidism and 7 patients had subclinical hyperthyroidism. **Interpretation and Conclusions:** Our study has decided that screening must be recommended for all MetS patients to rule out thyroid dysfunction. Both MetS and thyroid dysfunction are risk factors for cardiovascular disease (CVD).

KEYWORDS: Diabetes mellitus, Hypertension, Lipid profile, Metabolic syndrome, Obesity, Thyroid profile.

INTRODUCTION:

Metabolic syndrome (MetS) is a group of signs and symptoms which include abdominal obesity, elevated blood pressure (BP) and insulin resistance. It is related to increased risk of Type 2 Diabetes Mellitus, chronic kidney disease, cardiovascular disease is an important cause of mortality [1]. Initial detection of MetS is important because it raises the risk of cardiovascular disease between 1.5 to 1.8 times more and increase relative risk of coronary artery disease and 4.2 fold a death [2]. In persons with metabolic syndrome, the prevalence of cardiovascular disease increases 2-3 folds [3].

International Diabetes Federation (IDF) defines metabolic syndrome, as central obesity (defined as waist circumference (WC) ≥ 90 cm for men and ≥ 80 cm for women) along with presence of any two of the following [4].

- Increased triglyceride: ≥ 150 mg/dl.
- Decreased high density lipoprotein cholesterol (HDL-C): < 40 mg/dl in men, < 50 mg/dl in women.
- Systolic blood pressure (SBP) ≥ 130mm Hg or diastolic blood pressure (DBP) ≥ 85 mm Hg.
- Increased fasting blood Sugar (FBS) ≥ 100 mg/dl.

It has a complex pathogenesis in which various genetic and life style factor are involved [5]. The accumulation of body fat in an irregular or excessive manner is defined as obesity [6]. A key component of MetS is obesity which occurs due to raised in energy intake, reduced energy expenses or a combination of both, thus lead to positive energy balance [7]. In obese patients alterations of thyroid function were reported, long before the definition of MetS [8]. Thyroid hormones are altered due to obesity i.e. rises in TSH (Thyroid stimulating hormone) with no effect on T_4 (Thyroxine) and T_3 (Triiodothyronine) or rises in TSH and T_3 with no change in T_4 [7].

Thyroid disorder (hyperthyroidism or hypothyroidism) is divided as clinical or subclinical depending on the degree of clinical severity and the extent of abnormalities in thyroid indices [9]. Due to raised serum TSH, increased body mass index (BMI) and age are well known, to be positively related with BP [10]. Study has found that when BMI levels were 30 or above, the TSH levels were drastically more in comparison with the TSH level in patients with BMI 18.55 [8]. In a study done by Milionis et al. advocate that morbid obese females (BMI > 40 Kg/m^2) had increased TSH levels than other with moderate obesity (BMI < 40 kg $/m^2$). Decrease in FT_4 values were accompanied by increased BMI values. Study has evidenced that an increased levels of total (T_3), FT_3, total T_4 and TSH in morbidly obese subjects in comparison to control subjects [11].

Thyroid disorders and diabetes equally influence each other and relationship between both situations have long been reported. It has been seen that there was rise in the frequency of TD with increase in age and more prevalence in females compared to males and in diabetic subjects compared to non-diabetic subjects [12].

In an Indian study done by Bal et al., a prevalence of thyroid disease was found to be 40.4% among 184 type 2 diabetic patients, and was found positive correlation with age in the TD group [13]. In diabetes mellitus, patients with TD manifests either hyperthyroidism (clinical or subclinical) or hypothyroidism (clinical or subclinical) and is reflected in the circulating levels of thyroid hormones, namely thyroxine (T_4), tri-iodothyronine (T_3) and thyroid stimulating hormone (TSH) which might have an impact on blood glucose homeostasis [14]. In a study of Islam et al. it was found that patients with type 2 diabetes had considerable low FT_4 levels when compared with control subject [15].

A classical feature of MetS is high BP, and is a chief component of MetS and is found up to 1/3rd of hypertensive patients in western population [16]. Due to high BP, around 47 % of ischemic heart disease and 54% of stroke occurs. Increased risk of coronary artery disease occurs due to hypertension. It is an independent risk factor for cerebrovascular disease and cardiovascular disease [17]. An earlier study has reported that in MetS hypertension was associated with obesity [16].

Rise in serum TSH is well recognized to correlate with MetS having hypertension and cardiovascular disorders [18]. Hypothyroidism may be related with hypertension and conversely, that hypertension is related with hypothyroidism in a general consensus. A positive association among serum TSH and systolic and DBP has been found in Iqbal A et al. study [10].

Since 80 years back, the relation among thyroid hormone status and lipid parameters have been described. A study done by Waring et al. showed the odd ratio of rise in triglyceride and decrease HDL-C relative to thyroid function status. Overt and subclinical hypothyroidism were positively related to triglyceride levels where as decrease in HDL-C level were found in hyperthyroid as well as hypothyroid patients. Previous study advocate that increase triglycerides level were found around 1/3rd of all patients with overt hypothyroidism [19]. Kumar et al study found a positive correlation between T_3 with Total cholesterol, triglyceride, low density lipoprotein-cholesterol (LDL-C), HOMA-IR (Insulin resistance), insulin and negative correlation was found with body fat [20]. A higher level of LDL-C was found in subclinical hypothyroid patients and was positively correlated with TSH in Renuka et al. study [21].

AIMS & OBJECTIVES:

1. Selection of the MetS patients and control subjects.
2. Measurement of systolic and DBP, WC and BMI in MetS patients and control subjects.

3. Assay of blood sugar (FBS, PPBS), lipid profile, thyroid profile in MetS and control subjects.

MATERIAL AND METHODS:
The study has been conducted between February 2017 to August 2018

STUDY AREA: The present study was conducted in the department of Biochemistry in collaboration with department of Medicine, Maharishi Markandeshwar institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.

STUDY POPULATION:
Group 1: 300 subjects with MetS

Group 2: 300 healthy Volunteers controls (age and sex matched) without MetS.

Informed consent has been taken from the participants in the study.

ETHICAL CONSIDERATIONS: The proposed study has been approved by Institutional Ethics Committee vide letter no. **904** date 17.12.2016.

INCLUSION CRITERIA:
- Patients with MetS above 18 years of age.

EXCLUSION CRITERIA:
- Any history of liver disease
- Thyroid disease
- Familial hyperlipidemia
- Pregnancy
- Lactation
- Recovery from non thyroidal illness
- Cushing disease
- Renal disease
- Patients with history of chronic drug use (steroid treatment, antidepressant and anti psychotic drug user)
- Oral contraceptives

Waist Circumference Measurement: WC was measured with a tape in a horizontal plane, mid way between the inferior margin of the ribs and the superior border of the iliac crest.

SAMPLE COLLECTION:
5 ml of blood sample was aseptically collected as per the standard guidelines and protocol. Serum was allowed to separate and subsequently analyzed for various parameters as under-

Serum T_3, T_4, TSH, FT_3, FT_4 was assayed by chemiluminescence immunoassay Method, FBS, PPBS was assayed by glucose oxidase and peroxidase Method, Total cholesterol (cholesterol-oxidase), triglyceride (glycerol-oxidase-peroxidase), HDL-C (enzymatic assay), LDL-C and VLDL-C by Friedewald's calculation Method.

STATISTICALANALYSIS:
Data obtained was analysed by using SPSS 21 version software and results was compared in cases and controls. P value < 0.05 was taken as significant at 95% confidence intervals. Student's t-test and pearsons correlation coefficient was used to find the association between thyroid profile and various components of MetS (WC, blood glucose, BP, triglyceride, HDL-C).

RESULT:
The total number of patients in our study were 600 (100%) out of which 300 (50%) were healthy controls subjects and 300 (50%) with MetS patients were considered. Among 300 patients with MetS in the study 102 (34.0 %) were male and 198 (66.0 %) were female. Similarly there were 300 control subjects, out of which 102 (34.0 %) were male and 198 (66.0 %) were female.

Table I: Result of Anthropometric parameters amongst metabolic syndrome patients and control subjects

Parameters	Control	Case	P value
Age (Yrs)	52.79 ± 11.40	52.70 ± 10.98	0.526
BMI (Kg/m^2)	20.49 ± 2.24	29.43 ± 2.84	< 0.000
WC (cm)	80.49 ± 4.70	102.26 ± 7.92	< 0.000
SBP (mm Hg)	115.31 ± 6.62	148.26 ± 21.24	< 0.000
DBP (mm Hg)	76.31 ± 5.42	91.77 ± 10.96	< 0.000

BMI: body mass index; WC: waist circumference; SBP: Systolic blood pressure; Diastolic blood pressure P value < 0.05 are considered significant.

From the table I the mean and standard deviation (& SD) of age in the control subjects is 52.79 ± 11.40 years and for MetS patients is 52.70 ± 10.98 years. A statistically significant difference was not observed among two groups (p = 0.526). The mean (& SD) BMI of the control subjects is 20.49 ± 2.24 Kg/m^2 and for MetS patients is 29.43 ± 2.84 Kg/m^2. A statistically highly significant difference was observed among two groups (p < 0.000). The mean (& SD) WC of the control subjects is 80.49 ± 4.70 cm and for MetS patients is 102.26 ± 7.92 cm. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of SBP for control subjects is 115.31 ± 6.62 mm Hg. In MetS patients the corresponding mean and SD of SBP is 148.26 ± 21.24 mm Hg. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of DBP for control subjects is 76.31 ± 5.42 mm Hg. The corresponding mean and SD of DBP for MetS patients is 91.77 ± 10.96 mm Hg. A statistically highly significant difference was observed among two groups (p < 0.000).

Table II: Result of FBS, PPBS, lipid profile and thyroid profile amongst metabolic syndrome patients and control subjects

Parameters	Control	Case	P value
FBS (mg/dl)	79.35 ± 6.05	141.08 ± 56.02	< 0.000
PPBS (mg/dl)	103.08 ± 13.15	220.03 ± 98.34	< 0.000
TC (mg/dl)	164.30 ± 10.62	180.59 ± 28.08	< 0.000
TG (mg/dl)	126.26 ± 14.76	167.0 ± 50.92	< 0.000
HDL-C (mg/dl)	52.16 ± 6.33	37.79 ± 14.52	< 0.000
LDL-C (mg/dl)	86.87 ± 12.77	109.39 ± 29.24	< 0.000
VLDL-C (mg/dl)	25.25 ± 2.95	33.40 ± 10.18	< 0.000
T_3 (ng/ml)	0.99 ± 0.25	1.07 ± 0.63	< 0.000
T_4 (µg/dl)	6.96 ± 1.25	7.10 ± 3.08	< 0.000
TSH (µIU/ml)	2.32 ± 1.08	6.50 ± 7.75	< 0.000
FT_3 (pg/ml)	3.02 ± 0.43	2.88 ± 0.82	< 0.000
FT_4 (ng/dl)	1.24 ± 0.27	1.17 ± 0.39	< 0.000

FBS: Fasting blood sugar; PPBS: Post prandial blood sugar; TC: Total cholesterol; TG: triglyceride; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; VLDL-C: Very low density lipoprotein-cholesterol

P value < 0.05 are considered significant.

The table II shows that the mean and SD of FBS for control subjects is 79.35 ± 6.05 mg/dl. The mean and SD of FBS for MetS patients is 141.08 ± 56.02 mg/dl. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of PPBS for control subjects is 103.08 ± 13.15 mg/dl. The mean and SD of PPBS for MetS patients is 220.03 ± 98.34 mg/dl. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of total cholesterol (TC) for control subjects is 164.30 ± 10.62 mg/dl. The corresponding mean and SD for total cholesterol in MetS patients is 180.59 ± 28.08 mg/dl. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of triglyceride (TG) for control subjects is 126.26 ± 14.76 mg/dl. The corresponding mean and SD of triglyceride for MetS patients is 167.0 ± 50.92 mg/dl. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of HDL-C for control subjects is 52.16 ± 6.33 mg/dl. The corresponding mean and SD of HDL-C for MetS patients is 37.79 ± 14.52 mg/dl. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of LDL-C for control subjects is 86.87 ± 12.77 mg/dl. The corresponding mean and SD of LDL-C for MetS patients is 109.39 ± 29.24 mg/dl. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of VLDL-C for control subjects is 25.25 ± 2.95 mg/dl. The corresponding mean and SD of VLDL-C for MetS patients is 33.40 ± 10.18 mg/dl. A statistically highly significant difference was observed among two groups (p < 0.000).

The table II shows that the mean and SD of T_3 for control subjects is 0.99 ± 0.25 ng/ml. The corresponding mean and SD of T_3 for MetS patients is 1.07 ± 0.63 ng/ml. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of T_4 for control subjects is 6.96 ± 1.25 µg/dl. The corresponding mean and SD of T_4 for MetS patients is 7.10 ± 3.08 µg/dl. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of TSH for control subjects is 2.32 ± 1.08 µIU/ml. The corresponding mean and SD of TSH for MetS is 6.50 ± 7.75 µIU/ml. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of FT_3 for control subjects is 3.02 ± 0.43 pg/ml. The corresponding mean and SD of FT_3 for MetS patients is 2.88 ± 0.82 pg/ml. A statistically highly significant difference was observed among two groups (p < 0.000). The mean and SD of FT_4 for control subjects is 1.24 ± 0.27 ng/dl. The corresponding mean and SD of FT_4 for MetS patients is 1.17 ± 0.39 ng/dl. A statistically highly significant difference was observed among two groups (p < 0.000).

Table III: Thyroid status amongst metabolic syndrome patients and control subjects

	Euthyroid	Hypothyroidism	Hyperthyroidism	Subclinical hypothyroidism	Subclinical hyperthyroidism
Control (N=300)	300	0	0	0	0
Case (N=300)	171(57 %)	46 (15.33)	18 (6 %)	58 (19.33%)	7 (2.33%)

The table III shows that in a control subjects all 300 patients are in euthyroid state, and in case out of 300 patients 171 patients are in euthyroid state, 46 patients have hypothyroidism, 18 patients have hyperthyroidism, 58 patients have subclinical hypothyroidism and 7 patients have subclinical hyperthyroidism.

The pearson correlation analysis is given to assess relationship of components of Mets with thyroid profile. While significant negative correlation of HDL (r = -0.109; p=0.007) with T_3, FBS (r = -0.093; p = 0.022) with T_4, HDL (r = -0.089; p = 0.030) with T_4, HDL (r = -0.246; p = 0.000) with TSH, SBP (r = -0.128; p = 0.002) with FT_3, DBP (r = -0.087; p = 0.034) with FT_3, WC (r = -0.117; p = 0.004) with FT_4), FBS (r = -0.178; p = 0.000) with FT_3, SBP (r = -0.132; p = 0.001) with FT_4, DBP (r = -0.096; p = 0.019) with FT_4, WC (r = -0.085; p = 0.037) with FT_4, FBS (r = -0.168; p = 0.000) with FT_4 was found.

A positive correlation was observed between SBP ® =0.281; p = 0.000) with TSH, DBP (r =0.270; p = 0.000) with TSH, WC (r = 0.312; p = 0.000) with TSH, FBS (r = 0.231; p = 0.000) with TSH, TG (r = 0.207; p = 0.000) with TSH.

DISCUSSION:

It was noted from the results that TD was prevalent in 129 patients out of the 300 MetS patients, 46 patients having hypothyroidism, 18 patients having hyperthyroidism, 58 patients having subclinical hypothyroidism and 7 patients having subclinical hyperthyroidism. In our study TD was predominantly seen in females out of 198 females patients, 88 patients have TD similarly out of 102 male patients 41 have TD.

In our study the mean weight (76.58 ± 8.64) was significantly higher in MetS patients than in control groups (54.24 ± 7.45) p (<0.000). The mean height (161.18 ± 4.30) was significantly lower in MetS patients then in control groups (162.48 ± 4.16) p (<0.532).

In our study the mean BMI (29.43 ± 2.84) was significantly higher in MetS patients then in control groups (20.49 ± 2.24) p (<0.000). In our study the mean WC (102.26 ± 7.92) was significantly higher in MetS patients than in control groups (80.49 ± 4.70) p (<0.000).

In our study the mean SBP (148.26 ± 21.24) was significantly higher in MetS patients than in control group (115.31 ± 6.62) p (<0.000) similarly the mean DBP (91.77 ± 10.96) was significantly higher in MetS patients then in control group (76.31 ± 5.42) p (<0.000).

In our study the mean FBS (141.08 ± 56.02) was significantly higher in MetS patients when compared to control group (79.35 ± 6.05) p (<0.000). Similarly PPBS (220.03 ± 98.34) was also significance higher in MetS patients when compared to control group (103.08 ± 13.15) p (<0.000).

In our study the mean total cholesterol (180.59 ± 28.08) was significantly higher in MetS patients when compare to control group (164.30 ± 10.62) p (<0.000). The mean triglyceride (167.0 ± 50.92) was significantly higher in MetS patients when compared to control group (126.26 ± 14.76) p (<0.000). The mean HDL-C (37.79 ± 14.52) was significantly lower in MetS patients when compared to control group (52.16 ± 6.33) p (<0.000). The mean LDL-C (109.39 ± 29.24) was significantly higher in MetS patients when compared to control group (86.87 ± 12.77) p (<0.000). Rise in LDL-C level may be accompanied by raised formation of oxidized LDL-C contributing to enhanced risk of atherosclerosis. And the mean VLDL-C (33.40 ± 10.18) was also significantly higher in metabolic syndrome patients when compared to control group (25.25 ± 2.95) p (<0.000).

In our study a statistical significance of T_3 (1.07 ± 0.63) in MetS patients when compared to control group (0.99 ± 0.25) p (<0.000), T_4 (7.10 ± 3.08) in MetS patients when compare to control group (6.96 ± 1.25) p (<0.000), TSH (6.50 ± 7.75) in MetS patients when compared to control group (2.32 ± 1.08) p (<0.000), FT_3 (2.88 ± 0.82) in MetS patients when compared to control group (3.02 ± 0.43) p (<0.000), FT_4 (1.17 ± 0.39) in MetS patients when compared to control group (1.24 ± 0.27) p (<0.000).

In our study a positive correlation was observed between SBP, DBP, WC, FBS, TG with TSH and negative correlation between HDL with T_3; FBS,HDL with T_4; SBP,DBP, WC, FBS with FT_3 and SBP, DBP,WC, FBS with FT_4 was observed.

From our study it is evident that the thyroid disorders (hyperthyroidism or hypothyroidism) developed in MetS patients having hypertension, obesity, diabetes mellitus, dyslipidemia. This thyroid disorders may be due to effects of the different MetS parameters on thyroid hormone synthesis, or their secretion in the circulation.

CONCLUSION:

In our study, it is evident that thyroid disorder and MetS are correlated and thyroid disorder (hyperthyroidism or hypothyroidism) developed in (43%) MetS patients. In the study, the prevalence of hypothyroidism (34.6%) has been observed in MetS patients. Our study advocates that screening should be recommended for all metabolic syndrome patients to rule out thyroid dysfunction because associated thyroid dysfunction in metabolic syndrome patients can function as additional factors to predispose to cardiovascular complications in a patients of MetS. So early diagnosis of thyroid disorder in MetS patients, may be helpful for prevention of CV disease in MetS patients.

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