RELATIONSHIP BETWEEN THYROID STIMULATING HORMONE AND VARIOUS COMPONENTS OF METABOLIC SYNDROME

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ABSTRACT

Objective: To determine the relation between thyroid stimulating hormone and various components of metabolic syndrome.

Study Design: Descriptive cross-sectional study.

Place and Duration of Study: Pathology department, Army Medical College of National University of Sciences and Technology (NUST) Islamabad and Military Hospital (MH), Rawalpindi, Pakistan; from January to March 2013.

Material and Methods: Hundred adult inhabitants (30-60 years) of Rawalpindi participated in this study. Subjects who fulfilled the WHO criteria for metabolic syndrome (MetS) were included and those who had any thyroid illness, or were using any thyroid medications were excluded from this study. For thyroid function tests (TFT's), serum thyroid stimulating hormone (TSH), total tri-iodothyronine (TT3), free throxine (FT4) were estimated. Insulin resistance (IR) was measured by Homeostasis Model Assessment for IR (HOMA-IR). Data was analyzed by SPSS-18.

Results: Out of 50 subjects of control group, 26 (52%) were male and 24 (48%) were female. Basal metabolic rate (BMI), serum triglyceride (TG), HOMA-IR were higher and serum high density lipoprotein cholesterol (HDL-c) was lower in MetS patients. There was no significant difference in serum TT3 and FT4 between MetS patients and control group, however, mean serum TSH levels were higher in MetS (2.622 + 0.924 vs 5.002 + 1.074 mIU/l, $p<0.001$). In correlation analysis, serum TSH was positively and significantly correlated with BMI (r=0.344, $p=0.014$) and HOMA-IR (r=0.419, $p<0.002$).

Conclusion: These results suggest that serum TSH correlates with various components of metabolic syndrome patients. Analysis of serum TSH levels in metabolic syndrome patients may prove beneficial in preventing the various cardiometabolic complications in such patients.

Keywords: Body-mass index, Metabolic syndrome, Thyroid function tests.

INTRODUCTION

Metabolic syndrome hypothesized by Reaven[1] is a cluster of hyperglycaemia, hyperinsulinaemia, hypertension and dyslipidaemia[2]. Over the last two decades, there has been a striking increase in number of people with MetS[3]. Millions of people in developing countries are facing this burden as it is associated with a two- fold increased risk of CVD and a five- fold increased risk of DM[4]. Although prevalence of obesity is relatively low in Asia as compared to the developed countries, it is growing into a significant public health problem[5]. Common factors leading to this increasing epidemic are obesity, dyslipidaemia and insulin resistance which are also seen in combination in MetS[6].

Thyroid, which is the master gland of the body controls gene transcription, energy metabolism, growth and development by releasing two hormones known as T3 and T4. These hormones also effect blood pressure, glucose and lipid metabolism[7]. There is an increasing evidence that thyroid dysfunction is associated with obesity, so it is hypothesized that there might have an association between thyroid gland and metabolic syndrome[8]. Increase adipose tissue in MetS not only serve as a energy storage house, but also act as an interconnecting link between various target organs and central nervous system (CNS) by functioning as an endocrine organ[9]. Leptin, one of the important cytokines released by adipose tissue, interacts with the hypothalamic-pituitary-thyroid axis[10]. This adipocytokine (leptin) together with TSH is involved in

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causing abnormalities in thyroid function tests via insulin-like growth factor 1 (IGF-1)[11].

Studies have been done regarding this topic in developed countries, however, reported clinical data is scarce in Pakistan. This knowledge gap was addressed by designing a study to find the relationship between thyroid stimulating hormone and various components of metabolic syndrome like basal metabolic rate (BMI), HOMA-IR, serum triglyceride.

MATERIAL AND METHODS

This case control study was carried out in Pathology Department, Army Medical College of National University of Science and Technology (NUST) Islamabad and Military Hospital (MH), Rawalpindi, Pakistan (Jan-March 2013). Institutional Ethics Committee gave the permission of this project. 50 patients of MetS along with age and gender matched controls were included after obtaining their informed consent. WHO criteria was used for diagnosing the patients of MetS; which consist of insulin resistance (IR) plus any 2 of the following:

- BMI > 30 kg/m^2.
- Serum triglyceride ≥ 1.7mmol/l.
- Serum HDL cholesterol < 1.0 mmol/l in women and < 0.9 mmol/l in men.

Patients were excluded if they had any history of liver, thyroid, hematological and neoplastic diseases. Patients with infections, inflammatory and autoimmune diseases, familial hyperlipidaemia, pregnancy, lactation and those who were unable to give informed consent were also excluded.

Information regarding the demographic data (age, sex etc) and complete history was obtained and entered on a pre-designed proforma. Height was measured to the nearest centimeter (cm) with a standardized measuring chart and weight was measured to the nearest kilogram (kg) with a standardized scale without shoes. Body mass index (BMI) was calculated by the formula = weight (kg) / height (m^2).

Ten ml of fasting venous blood sample was collected under sterile conditions and equal amounts were transferred to a plain vacutainer for serum analysis and EDTA tube for plasma analysis. Serum was separated by centrifugation for 15 minutes. Routine investigations was done on the same day. The serum for insulin measurements was stored at -20^0 C , until the biochemical analysis.

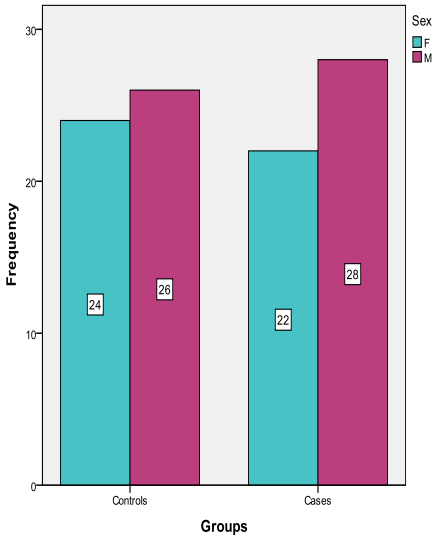

Figure-1: Comparison of gender between control and cases of metabolic syndrome.

Plasma glucose, serum triglyceride (TG), plasma high density cholesterol (HDL-c) were estimated by the enzymatic colorimetric method by using Globe diagnostic kits on fully automated chemistry analyzer (Selectra-E).Controls were run with each run.

Thyroid hormones (TSH, TT3, FT4) and Insulin were measured on Access-2 immunoassay (Beckman Coulter) based on principle of chemiluminance. Insulin resistance (IR) was measured by Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) by the following formula:

HOMA-IR= fasting plasma glucose (mmol/l) × fasting plasma insulin (µIU/ml) / 22.5 (Value > 2.5 was considered as evidence of insulin resistance).

Data had been analyzed using Statistical Package for the Social Sciences (SPSS) version-18. Descriptive statistics were used to describe the data. Independent samples t-test was applied to compare the variables between the groups. Pearson correlation coefficient was calculated to study the relationship of TSH with different variables. A *p*-value < 0·05 was considered to indicate statistical significance.

RESULTS

This study included 100 patients. Among the 50 MetS patients, 28 (56%) were male and 22 (44%) were female while in control group, 26 (52%) were male and 24 (48%) were female (Figure-1). BMI, serum TG, HOMA-IR were higher and plasma HDL-c was lower in group of MetS. Regarding the thyroid function tests, there was no significant difference in serum TT3 and FT4 between MetS and control group, however, mean serum TSH levels were higher in MetS (2.622 + 0.924 vs 5.002 + 1.074 mIU/l, p<0.001) as shown in Table-1.

Table-1: Comparison of variables between metabolic syndrome cases and controls.

	Cases Mean and SD	Controls Mean and SD	*p*-value
Age	44.30 ± 7.88	45.24 ± 7.99	0.555
Body-mass index (BMI, unit: kg/m^2)	29.64 ± 1.72	22.70 ± 1.03	< 0.001
Fasting plasma Glucose (mmol/l)	7.10 ± 0.896	4.33 ± 0.629	< 0.001
Fasting plasma Insulin (µIU/ml)	28.77 ± 1.96	11.77 ± 1.12	< 0.001
HOMA-IR	9.15 ± 1.77	2.24 ± 0.206	< 0.001
Serum Triglyceride (TG, unit: mmol/l)	4.304 ± 1.500	1.009 ± 0.302	< 0.001
Plasma High density lipoprotein cholesterol (HDL-c, unit: mmol/l)	0.763 ± 0.098	2.507 ± 0.382	< 0.001
Serum Total tri-iodothyronine (TT3, unit: nmol/l)	2.108 ± 0.410	1.890 ± 0.363	0.006
Serum Free throxine (FT4, unit: pmol/l)	81 ± 1.914	15.38 ± 3.350	< 0.001
Serum Thyroid stimulating hormone (TSH, unit: mIU/l)	5.002 ± 1.074	2.622 ± 0.924	< 0.001

Table-2: Correlation of TSH with various components of metabolic syndrome.

	r-value	*p*-value
Body-mass index (BMI, unit: kg/m^2)	0.344	0.014
HOMA-IR	0.419	0.002
Serum Triglyceride (TG, unit: mmol/l)	0.412	0.003
Plasma High density lipoprotein cholesterol (HDL-c, unit: mmol/l)	-0.344	0.014

When correlation analysis (Table-2) was performed to find the relationship of serum TSH with various components of MetS, the results showed that serum TSH was positively and significantly correlated with BMI (r=0.344, p=0.014) HOMA-IR (r=0.419, p<0.002) and serum Triglyceride (r=0.412, p=0.003).

DISCUSSION

Metabolic syndrome is a multiplex disorder consisting of hypertension, dyslipidaemia, obesity and abnormal glucose and insulin metabolism[12]. This syndrome doubles the risk of cardiovascular diseases whereas the risk of developing Type-2 DM increases to 5-fold[13]. Patients with metabolic syndrome also suffer abnormalities in their thyroid function tests (TFT's)[14]. Moreover, many studies support the fact that widespread and fundamental metabolic effects of thyroid hormones are associated with various components of MetS[15,16]. Significant changes in thyroid function tests that occur in MetS patients suggest a direct relationship between adiposity that occur in metabolic syndrome and derangement that adiposity cause in hypothalamic-pituitary-thyroid axis[17]. Study has been done emphasizing the significance of thyroid function test in newly diagnosed cases of Metabolic syndrome as increased frequency

of thyroid disorders has been observed in MetS patients[18].

The most important finding in our study is the elevated serum TSH levels, however, the levels of serum TT3 and FT4 remains within the reference interval in MetS patients (Table-1). Studies supporting these findings also indicates a higher level of serum TSH and within normal reference range values of TT3 and FT4 in morbidly obese people[19,20]. Study done in Chinese population, however, documented not only the raised levels of TSH, but also low levels of serum FT4 has been observed in patients of metabolic syndrome[21]. Whereas both the levels of serum TT3 and FT4 were in the lower reference interval in another study[22].

In correlation analysis, a significant positive correlation of serum TSH with various components of MetS like basal metabolic rate (BMI) and HOMA-IR has been found in MetS patientsPrevious studies also established a positive correlation of serum TSH with basal metabolic rate BMI, HOMA-IR and serum triglycerides[13,23]. In this study, as serum TT3 and FT4 remain in the nomal reference interval, so this study unable to establish any relation of either TT3 and FT4 with the various components of MetS. Other studies in which low levels of serum FT4 along with elevated levels of serum TSH has been found, also establish a positive correlation of both the serum TSH and FT4 with MetS components[24,25]. Elevated levels of serum TSH and within the reference interval serum TT3 and FT4 in our study suggest a state of subclinical hypothyroidism (SHO) in metabolic syndrome patients. Hypothyroidism and metabolic syndrome are well-recognized risk factors for various cardiovascular diseases[26]. Insulin resistance (IR) as shown by the significantly raised values of HOMA-IR (also one of the WHO diagnostic criteria of MetS) has been reported for the first time in 2009 by Eirini et al., in patients of subclinical hypothyroidism[27,28]. There is no agreed upon cut-off value for insulin resistance, however, a value > 2.5 may be considered as evidence of insulin resistance[29,30,31]. Another study also shows that insulin resistance (IR) is one of the important laboratory finding seen in subclinical hypothyroidism[32]. Study by Semra et al., showed that elevated serum TSH levels in MetS patients is further involved in causing the proliferation of thyroid follicles[9]. A positive and significant correlation was found between serum TSH and thyroid volume[23].

CONCLUSION

This study concludes that serum TSH correlates positively with various components of metabolic syndrome patients like BMI, HOMA-IR and serum TG, whereas a negative correlation has been observed with plasma HDL-c. Analysis of serum TSH levels in metabolic syndrome patients may prove beneficial in preventing the various cardiometabolic complications, as these patients are at an increased risk of going into a state of subclinical hypothyroidism.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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