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An observational assessment of clinic-epidemiological factors of thyroid dysfunction (TD) in patients diagnosed with metabolic syndrome (MetS)

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Abstract
Aim: The aim of the present study was to assess the prevalence and clinical and epidemiological factors of thyroid dysfunction (TD) in patients diagnosed with metabolic syndrome (MetS).
Methods: The study was conducted in the Department of Medicine. The study protocol was approved by local independent ethics committees. In this study, we had enrolled 400 patients with MetS. The study was conducted in accordance with the principles of the Declaration of Helsinki, International Council on Harmonization Good Clinical Practice (ICH GCP) guidelines, and Indian regulatory guidelines (Indian Council of Medical Research and Indian GCP guidelines).
Results: In this study, we had enrolled 400 patients with MetS. The baseline demographic characteristics of these patients are shown. Of all the enrolled patients, 120 (30%; 95% CI: 23.83-32.32) were diagnosed with TD (mean age (SD): 47.9 (10.96) years; mean BMI: 30 ± 4 94 kg/m2), with a higher prevalence among women compared to men (91 (75%) vs. 30 (25%)). Of the 400 MetS patients, overt hypothyroidism was reported in 78 (19.5%) patients and overt hyperthyroidism in 8 (2%) patients.

Keywords: Metabolic syndrome, hypothyroidism, subclinical hypothyroidism, thyroid dysfunction

Introduction

According to available studies, 25 - 35% of the adult population in India is affected by metabolic syndrome [1]. According to the National Cholesterol Education Programme Adult Treatment Panel–III guidelines, metabolic syndrome is diagnosed when a patient has at least 3 of the following five conditions [2]. Increased mechanisation, decreased physical activity, consumption of fat-rich, fast and junk food has resulted in an increased prevalence of obesity and insulin resistance giving rise to metabolic syndrome. Non-communicable disease (NCD) prevalence rates are very high in subjects with metabolic syndrome [3, 4]. Early identification of factors predictive of metabolic syndromes like hypertension and obesity and remedial measures will help in the prevention of NCD like diabetes and cardiovascular disease.

Metabolic syndrome and thyroid dysfunction association was demonstrated in many recent studies. Thyroid dysfunction is altered states of thyroid-stimulating hormone level with or without alteration in Tri iodothyronine (T3), Tetra iodothyronine (T4). People with high Thyroid-stimulating hormone (TSH) levels were found to have a two-fold rise in the prevalence of metabolic syndrome [5]. Subclinical hypothyroidism with increased TSH level was also seen to be associated with increased risk of coronary heart disease. Both atherosclerosis and dyslipidaemia are common in hypothyroidism [6]. MetS is closely associated with thyroid dysfunction (TD) due to the impact of thyroid hormones on lipid metabolism, glucose, blood pressure, and cardiovascular dysfunction [7]. Functional changes in the thyroid gland might have an association with MetS and its related components including obesity, insulin resistance (IR), lipid and glucose metabolism abnormalities, raised blood pressure, and cardiovascular dysfunction. MetS and TD are both characterized by a cluster of common abnormalities such as abdominal obesity, hyperglycemia, hypertension, reduced high-density lipoprotein cholesterol (HDL-C), and elevated triglycerides (TG). Moreover, IR, identified as a basic mechanism for MetS, also plays a role in hypothyroidism [8]. The occurrence of both the conditions may be compounded to increase the risk for cardiovascular diseases (CVDs).

Both metabolic syndrome and hypothyroidism are independent risk factors for cardiovascular diseases (CVD). Presence of both conditions may be compounded to increase the risk for CVD and a considerable overlap occurs in the pathogenic mechanisms of atherosclerotic cardiovascular disease by metabolic syndrome and hypothyroidism [9].

The aim of the present study was to assess the prevalence and clinical and epidemiological factors of thyroid dysfunction (TD) in patients diagnosed with metabolic syndrome (MetS).

Methods

The study was conducted in the Department of Medicine. The study protocol was approved by local independent ethics committees. In this study, we had enrolled 400 patients with MetS. The study was conducted in accordance with the principles of the Declaration of Helsinki, International Council on Harmonization Good Clinical Practice (ICH GCP) guidelines, and Indian regulatory guidelines (Indian Council of Medical Research and Indian GCP guidelines).

Patients aged 18 to 65 years, with an established diagnosis of MetS based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria (with modified waist), with or without known TD, were invited to participate in the study during their routine clinical visit to the endocrinologists, gastroenterologists, and/or hepatologists. Pregnant patients or patients with a

history of jejunoileal bypass, biliopancreatic diversion, extensive small bowel resection, total parenteral nutrition, any forms of chronic liver disease, hepatocellular carcinoma, patients on weight loss therapies or steatogenic drugs, and known HIV-positive cases were excluded from the study. At the screening visit, the following data were collected in the case report forms: demographics, anthropometric measurements, significant medical (including FPG, serum TG, and HDL-C values from patients' medical records) and surgical history, family history, lifestyle parameters, history of consumption of any obesogenic medicines, vital signs, and details of physical examination.

After obtaining an informed signed consent to participate in the study, the eligible patients from the screening visit were requested to visit the clinic after an overnight fast within 3-10 days of consenting. At this visit (visit 1), abdominal ultrasound examination (USG) was performed in patients who did not consume alcohol or consumed less than 20 g of alcohol per day and had not received corticosteroids, amiodarone, or tamoxifen. Blood samples were collected for assessment of hemogram, coagulogram (activated partial thromboplastin time, thrombin time, and prothrombin time), plasma insulin, plasma glucose, lipid profile (TG, total cholesterol (TC), HDL-C, and low-density lipoprotein cholesterol (LDL-C)), and thyroid function (free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH)). The fasting plasma glucose and plasma insulin were used for the calculation of homeostatic model assessment-established IR (HOMA-IR). The patients were followed up for a mean of one year to check for new diagnoses of TD.

The primary endpoint was the prevalence of TD among patients with MetS. Other endpoints included the percentage of patients with hyperthyroidism, subclinical hyperthyroidism, hypothyroidism, and subclinical hypothyroidism and percentage of patients with TD with respect to individual components of MetS (waist circumference, TG, HDL-C, SBP, DBP, and fasting glucose) and IR (HOMA − IR > 1 64).

Statistical Analysis

All statistical analyses were performed using SAS® version 9.2 (SAS Institute Inc., USA). The prevalence of TD in MetS patients was calculated as a number and percentage with 95% CI.

Results

Table 1: Demographics and baseline characteristics of 432 patients with metabolic syndrome

Parameter	Age ≤ 45 y (N = 180)	Age > 45 y (N = 220)	Total (N = 400)
Age in years			
Mean (SD)	36.4 (6.08)	55.5 (5.52)	47.3 (10.96)
Range	21.0-45.0	46.0-65.0	21.0-65.0
Gender			
Women, N (%)	110 (61.12%)	120 (54.54%)	230 (57.5%)
Men, N (%)	70 (38.88%)	100 (45.46%)	179 (42.5%)
Height in cm, mean (SD)	163.0 (9.02)	160.8 (8.44)	161.7 (8.74)
Weight in kg, mean (SD)	79.4 (13.13)	75.8 (12.29)	77.3 (12.75)
Waist circumference in cm, mean (SD)	98.5 (9.41)	98.7 (9.92)	98.6 (9.70)
Hip circumference in cm, mean (SD)	106.3 (11.07)	104.7 (11.14)	105.4 (11.13)

In this study, we had enrolled 400 patients with MetS. The baseline demographic characteristics of these patients are shown. Of all the enrolled patients, 120 (30%; 95% CI: 23.83-32.32) were diagnosed with TD (mean age (SD): 47.9 (10.96) years; mean BMI: 30 ± 4 94 kg/m2), with a higher prevalence among women compared to men (91 (75%) vs. 30 (25%)).

Table 2: Percentage prevalence of different grades of thyroid dysfunction

Classification of TD	MetS patients (N = 400) N (%)
Hypothyroidism	70 (17.5)
New overt hypothyroidism	8 (2)
New subclinical hypothyroidism	40 (10)
Hyperthyroidism	8 (2)
New overt hyperthyroidism	0
New subclinical hyperthyroidism	4 (1)
Total number of TD patients	120 (30)

Of the 400 MetS patients, overt hypothyroidism was reported in 78 (19.5%) patients and overt hyperthyroidism in 8 (2%) patients.

Discussion

Metabolic syndrome is a constellation of abnormalities, including increase in weight (obese), having hypertension, abnormal lipid profile with elevated triglycerides and low values of high-density lipoproteins, increased values of fasting blood sugars. Patients of metabolic syndrome had a higher risk of developing diabetes and cardiovascular diseases in future. Thyroid dysfunction is common among patients of metabolic syndrome. In various studies conducted in India, Nepal, Middle East and African countries the prevalence of thyroid dysfunction in metabolic syndrome patients is in the range of 21- 51% [10-12]. Metabolic syndrome can be associated with endocrine and non-endocrine disorders and has widespread consequences. Alterations in thyroid functions, though well known, are not recognized clinically and there is inconsistency in thyroid functions in metabolic syndrome [13].

Oxidative stress, chronic inflammation, and angiogenesis are believed to enhance the pathogenesis of MetS [14]. The important components of MetS, such as hyperglycemia and inflammation, upsurge the production of reactive oxygen species (ROS) resulting in increased oxidative stress with overactivation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [15, 16]. The main ROS is the superoxide anion, produced by NADPH oxidase. Hypermetabolic state in hyperthyroidism may accelerate free radical production in mitochondria and induce changes in the antioxidant defense system. In hypothyroidism, associated oxidative stress is the consequence of reduced capacity of the antioxidative defense.

The lesser number of subclinical hypothyroidism cases (10%) reported in our study could be attributed to the high enrolment of patients with known cases of hypothyroidism (17.5%), who were already on levothyroxine therapy. The overall rate of hypothyroidism at baseline (17.5%) plus new

overt hypothyroidism (2%) and new subclinical hypothyroidism (10%) was calculated as 25.70%. In agreement with our findings, a similar prevalence of hypothyroidism was reported in MetS population in other Indian studies as well, *viz*, Kota *et al*. (26%) [17].

In our study, women with MetS had a higher incidence of TD in comparison to men. Both men and women in the higher age group (>45 years of age) had a higher incidence of TD. Our results were in agreement with other reports where there was a tendency of increasing TD with aging across both genders [18, 19]. Thus, age and gender could represent significant risk factors for TD in MetS patients, prompting a detailed clinical and laboratory evaluation in these groups.

In this study, the MetS components observed in patients diagnosed with TD were high waist circumference, reduced HDL-C, raised HOMA-IR, systolic blood pressure, diastolic blood pressure, fasting glucose, and TG. A higher proportion of females had waist circumference above the cutoff (>80 cm) as compared to men. Though the other studies have also reported an association between TD and components of MetS, but it is still debatable. A Nigerian study reported MetS to be significantly associated with higher FT4 [20]. Kota *et al*. found the significant association between subclinical hypothyroidism and MetS with the relationship between TSH levels and TC, TG, LDL, and HDL-C levels among Indian patients.[17] It should be noted that while exploring the relationship between TD and components of MetS, most studies have focused on the subclinical hypothyroidism. Further, it should be noted that the pattern of TD in MetS and its relationship with components may vary upon geographic locale, age, gender, diet, and genetics, and environmental factors [21, 22].

Conclusion

Thyroid dysfunction is an important entity as a complication in metabolic syndrome patients. From various studies, it is a known fact that the incidence of thyroid hormone abnormality is more in females as compared to males. The prevalence of TD in patients with MetS was high, indicating a possible interplay between thyroid status and MetS. The data generated from the present study will aid in establishing a correlation between TD and MetS in Indian patients. This early diagnosis of TD in MetS would help in modifying the disease course by early interventions with appropriate lifestyle modification regimens, as applicable. However, future large sample-sized prospective studies are warranted which could evaluate the impact of TD management in terms of reduction in MetS and its related components.

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