Global Academic Journal of Medical Sciences

Available online at www.gajrc.com
DOI: 10.36348/gajms.2021.v03i06.005

OPEN ACCESS

ISSN: 2706-9036 (P)
ISSN: 2707-2533 (0)

Original Research Article

"Association Between Subclinical Hypothyroidism and Metabolic Syndrome-A Case-Control Study"

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Article History
Received: 02.11.2021
Accepted: 06.12.2021
Published: 12.12.2021

Abstract: Introduction: Subclinical hypothyroidism (ScH) is an endocrine alteration that is related to cardiovascular risk factors, including those categorized as components of the Metabolic Syndrome (MS). However, findings in prior reports regarding an association between these alterations are inconsistent. Metabolic syndrome is now considered as global epidemic and for last few decades MetS is highly prevalent in Bangladesh. **Objective:** To determine the metabolic syndrome is associated with subclinical hypothyroidism. **Materials & Methods:** The present case-control study was conducted in the Department of Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh over a period of one year between January 2020 to February 2021. Patients of metabolic syndrome were considered as case, while apparently healthy individuals (having no hypertension, central obesity or dyslipidaemia) were taken as control. Metabolic syndrome was defined as having at least three criteria out of five criteria, as recommended by NCEP: ATPIII Diagnostic Criteria for Metabolic Syndrome, while subclinical hypothyroidismwas defined, when TSH ranges from 4-20 mU/L with normal FT3 and FT4. During the study period, while friends and relatives of cases of similar age and sex were selected as control. **Results:** A total of 71 cases and 71 controls were consecutively included in the study. In the present study out of 71 cases 49(69.01%) had central obesity (waist circumference > 90 cm for male and > 80 cm for female), 57(81.4%) had raised triglycerides (TG ≥ 150 mg/dl), 61(87.1%) had raised blood pressure (≥130/85), 60(84.51%) had hyperglycemia (fasting blood glucose ≥ 100 mg/dl) and only 12(16.90%) had reduced HDL (< 40 mg/dl for male and < 50 mg/dl for female) three factors, namely subclinical hypothyroidism , BMI and socioeconomic status were observed to be significantly associated with metabolic syndrome in univariate analysis. After adjustment by binary logistic regression analysis, all these three variables remained to be significantly associated with metabolic syndrome with risk of having the condition being 2.3(95% CI = 0.9–5.8) times more in patients with subclinical hypothyroidism,

2.3(95% CI = 1.4–8.1) times higher in overweight/obese individuals and 2.8(95% CI = 1.3–5.8) times higher in affluent socioeconomic class (p=0.038, p=0.007 and p=0.006 respectively). The present study revealed that subclinical hypothyroidism significantly associated with MetS. Subclinical hypothyroidism carries more than 2-fold higher risk of having MetS.**Conclusion:** The study found that factors, namely subclinical hypothyroidism, BMI and socioeconomic status to be significantly associated with metabolic syndrome in univariate analysis. After adjustment by binary logistic regression analyses, patients of metabolic syndrome carry more than 2.7-fold higher risk of having subclinical hypothyroidism.

Keywords: Subclinical Hypothyroidism, Metabolic Syndrome, BMI, Risk Factor.

I. INTRODUCTION

Metabolic Syndrome (MS) is defined as a "constellation" of cardiometabolic risk factors, which, jointly, increase the risk of suffering cardiovascular diseases and type 2 diabetes mellitus [1]. The worldwide prevalence of metabolic syndrome in the adult population is on the rise and Bangladesh is not an exception [2]. Metabolic syndrome is defined by a constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of cardiovascular disease, type 2 diabetes mellitus, and all causes of mortality. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors which constitute the syndrome [3]. Current estimates revealing that about 20-30% of adult population worldwide affected by this syndrome [4]. On the other hand, subclinical hypothyroidism (ScH) is defined by high thyroid stimulating hormone (TSH) levels with normal free thyroxine (T4) [5]. Although it has been associated with coronary and carotid arterial disease, the association between ScH and MS and its individual components is currently a controversial subject. There are inconsistent results as regards to the triggers of thyroid disruptions, aside from the autoimmune etiological process, the cut-off values for its diagnostic and the temporary association with individual effects of some metabolic alterations on its development [6]. The prevalence of metabolic syndrome has increased greatly not only in industrialized nations [7], but also in developing countries as well [8]. In some populations or segments of the population, the prevalence is even higher and its prevalence has been documented as 11–41% [9]. On the other hand, in parts of developing world in which young adults predominate, the prevalence is lower but with increasing affluence and aging of the population, the prevalence undoubtedly is on the rise [8]. Prevalence of metabolic syndrome in USA has been found to be 23.7% [7]. In a multiethnic study in Singapore, 28.8% of Indian, 24.2% of Malaysian 14.8% of Chinese had metabolic syndrome [10]. In Bangladesh the weighted pooled prevalence of metabolic syndrome regardless of gender and criteria used to define metabolic syndrome is 30.0% with high heterogeneity observed. Subclinical hypothyroidism (SCH) is an asymptomatic condition characterized by normal thyroid hormone levels accompanied with high levels of thyroid stimulating hormone (TSH) [11]. It is a prevalent condition among adult population; however, it is frequently overlooked [12]. SCH has also been suggested as a risk factor for atherosclerotic cardiovascular disease and metabolic disorders such as hyperlipidemia, hypertension, low grade inflammation and hypercoagulability may accompany this process [13-15]. As Patients with subclinical hypothyroidism are at an increased risk for atherosclerosis and cardiac manifestations and thus, the thyroxin replacement in these patients has a beneficial effect on the low-density lipoprotein cholesterol levels and the clinical symptoms of hypothyroidism [16].

II. MATERIALS & METHODS

The present case-control study was conducted in the Department of Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh over a period of one year between January 2020 to February 2021. Patients of metabolic syndrome were considered as case, while apparently healthy individuals (having no hypertension, central obesity or dyslipidaemia) were taken as control. Metabolic syndrome was defined as having at least three criteria out of five criteria, as recommended by NCEP: ATPIII Diagnostic Criteria for Metabolic Syndrome, while subclinical hypothyroidism was defined, when TSH ranges from 4-20 mU/L with normal FT3 and FT4. During the study period, while friends and relatives of cases of similar age and sex were selected as control.

Study population

Patients of metabolic syndrome were considered as case, while apparently healthy individuals were taken as control. In this study 71 patients of MetS were selected as case and 71 apparently healthy individuals were considered as control.

Inclusion criteria

The individuals with following characteristics were included in the study:
All cases of metabolic syndrome patients who are diagnosed on the basis of NCEP: ATP III criteria and are 18 years or older as cases.

Apparently healthy individuals who were 18 years or above and did not have hypertension, diabetes mellitus or central obesity and were willing to participate in the study as control.

Exclusion criteria

Individuals with following characteristics were excluded:

- Known case of thyroid diseases
- Known case of any acute illness or chronic illness like chronic heart failure, chronic renal failure and chronic liver disease
- Pregnancy
- Patients chronically taking steroid, antipsychotics, hormonal replacement therapy (HRT) and other medications that alter thyroid function

DATA COLLECTION PROCEDURE

Data were collected on variables of interest using the semi structured questionnaire containing the variables of interest. Both indoor and outdoor basis patient's data were collected. All cases of metabolic syndrome patients who were diagnosed on the basis of NCEP: ATP III criteria selected as case and persons who did not have hypertension, diabetes mellitus or central obesity were selected as control. The studied variables were age, gender (male and female) occupational status, blood pressure, waist circumference, BMI, blood glucose, thyroid function test, lipid profile. Data were collected by face to face interview. The diagnosis of MetS was attained using protocol described by National Cholesterol Education Program Adult Treatment Panel III which considers that the patient has MetS when three or more risk factors described below are Increased waist circumference, Men: > 40 inches (EURO)/35 inches (SA),Women: > 35 inches (EURO)/31.5 inches (SA),elevated triglycerides > 150 mg/dL or drug treatment for elevated triglycerides, reduced HDL-C Men: < 40 mg/dL ,Women:<50 mg/dL, Elevated blood pressure > 130/85 mm Hg or drug treatment for elevated blood pressure, elevated fasting glucose> 100 mg/dL or drug treatment for elevated glucose.

Data processing and statistical analysis

Data were processed and analyzed using statistical soft-ware SPSS (Statistical Package for Social Sciences), version 25.0. Both descriptive and inferential statistics were used to analyze the data. Prevalence of subclinical hypothyroidism and other confounding variables were compared between case and control groups using Chi-squared ($\chi 2$) test, while continuous variables were compared between groups using unpaired t-Test. As more than one factors were found associated with metabolic syndrome in univariate analysis, binary logistic regression analysis was done to find the independent predictors of metabolic syndrome. The level of significance was set at 5% and p-value less than 0.05 was considered statistically significant.

III RESULTS

Total of 71 cases (patients of metabolic syndrome) and an equal number of controls (patients without metabolic syndrome). All the demographic and clinical characteristics were then compared between the two groups to find out the association of subclinical hypothyroidism with metabolic syndrome. After adjustment by binary logistic regression analysis, all these three variables persisted to be significantly associated with metabolic syndrome with risk of having the condition being 2.3(95% CI = 0.9 – 5.8) times higher in subclinical hypothyroidism, 2.3(95% CI = 1.4 – 8.1) times higher in overweight/obese individuals and 2.8(95% CI = 1.3 – 5.8) times more in patients with affluent socioeconomic class (p = 0.038, p = 0.007 and p = 0.006 respectively). The findings obtained from the study are presented below:

Table I. Association between demographic characteristics and metabolic syndrome.

Demographic characteristics	Group	
	Case (n = 71)	Control (n = 71)
Age (yrs)#	55.5 ± 10.5	50.8 ±10.4
Sex*		
Male	33(42.25%)	30(42.25%)
Female	38(53.52%)	41(57.75%)
Residence*		
Rural	30(42.25%)	33(42.25%)
Urban	41(57.75%)	38(53.52%)
Occupation*		
Business, service & housewife	54(76.06%)	53(74.65%)
Farming, labour & others	17(23.94%)	18(25.35%)
Socioeconomic status*		
High class/ rich	38(53.52%)	21(29.58%)
Poor & middle class	33(42.25%)	50(70.42%)

Figures in the parentheses indicate corresponding %;
*Chi-squared Test (χ^2) was done to analyze the data.
Data were analyzed using unpaired t-Test and were presented as mean ± SD.

Analyses of association between demographic characteristics and metabolic syndrome revealed that cases were relatively older than the controls. There was no significant difference between case and control groups in terms of sex, residence and occupation. Cases more often belonged to affluent class (upper middle class and rich) than did the controls.

Table II. Distribution of cases by their metabolic syndrome components.

Variables	Frequency	Percentage
Central obesity	49	69.01
Reduced HDL	12	16.90
Raised triglycerides	58	81.69
Elevated blood pressure	62	87.32
Hyperglycemia	60	84.51

*Total will not correspond to 100% for multiple responses.

Of the 71 cases 49(69.01%) had central obesity (waist circumference > 90 cm for male and > 80 cm for female), 58(81.69%) had raised triglycerides (TG ≥ 150 mg/dl), 62(87.32%) exhibited raised blood pressure (≥ 130/85), 60(84.51%) had hyperglycemia (fasting blood glucose ≥ 100 mg/dl) and only 12(16.90%) had reduced HDL (< 40 mg/dl for male and < 50 mg/dl for female) (Table II).

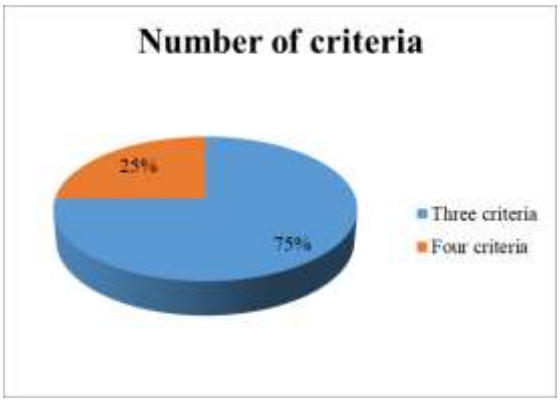

Fig. 1: Distribution of cases by number of criteria of metabolic syndrome present in them.

Over three-quarters (75%) of the cases had three criteria of MetS and the rest 25% had four criteria (Fig. 1).

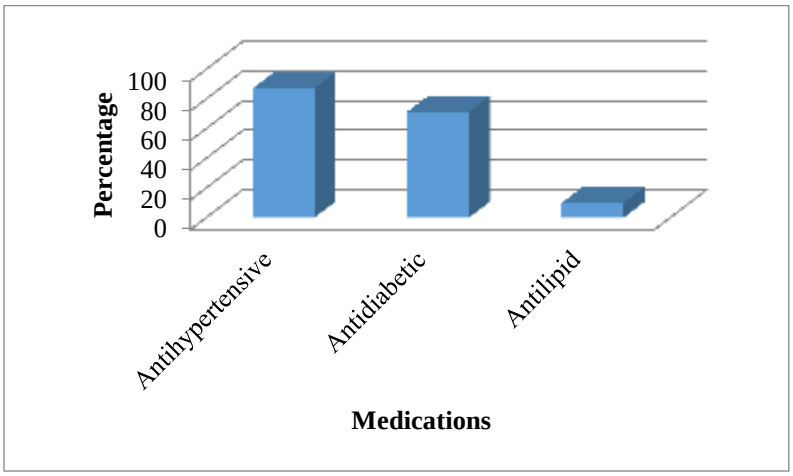

Fig. 2: Distribution of cases by medications used.

Majority (87.1%) of the cases was under antihypertensive drugs, 71.4% were under antidiabetic drugs and only 10% were receiving anti-lipid drugs (Fig. 2).

Table III. Association between BMI and metabolic syndrome.

Demographic characteristics	Group		p-value	Odds Ratio (95% CI of OR)
	Case (n = 71)	Control (n = 71)		
BMI (kg/m^2)*				
Overweight & obese	61(85.91%)	47(66.20%)	0.006	3.1(1.3 – 7.2)
Normal	10(14.09%)	24(33.80%)		
Mean ± SD	27.7 ± 3.1	26.0 ± 2.5		

Figures in the parentheses indicate corresponding %;
*Chi-squared Test (χ^2) was done to analyze the data.

Majority (85.91%) of the cases was overweight or obese compared to 66.20% of the control group (p = 0.006). Overweight and obese individuals carry more than 3-fold (95% CI= 1.3 – 3.9) higher risk of developing metabolic syndrome than the individuals with normal BMI (Table III).

Table IV. Association between subclinical hypothyroidism and sex.

Subclinical hypothyroidism	Sex		p-value	Odds Ratio (95% CI of OR)
	Female (n = 79)	Male (n = 63)		
Present	18(25.35%)	8(11.27%)	0.124	2.0(0.8 – 5.0)
Absent	61(74.65%)	55(88.73%)		

Figures in the parentheses indicate corresponding %;
*Chi-squared Test (χ^2) was done to analyze the data.

The prevalence of subclinical hypothyroidism was much higher in females (25.35%) than that in males (11.27%) (p = 0.124). The risk of having subclinical hypothyroidism in females was found to be 2(95% CI = 0.8 – 5.0) times higher than that in males (Table IV).

Table V. Association between subclinical hypothyroidism and metabolic syndrome.

Subclinical hypothyroidism	Group		p-value	Odds Ratio (95% CI of OR)
	Case (n = 71)	Control (n = 71)		
Present	18(25.35%)	8(11.27%)	0.030	2.7(1.1 – 6.6)
Absent	53(74.65%)	63(88.73%)		

Figures in the parentheses indicate corresponding %;
*Chi-squared Test (χ^2) was done to analyze the data.

Subclinical hypothyroidism demonstrated their significant presence (25.35%) among cases than that among controls (11.27%) (p = 0.030). The risk of having subclinical hypothyroidism among metabolic syndrome patients (case) 2.7 times more than the non-metabolic syndrome patients (control) which is implied by odd ratio 2.7(95% CI = 1.1 – 6.6). (Table- V)

IV. DISCUSSION

In this study subclinical hypothyroidism demonstrated their significant presence (25.35%) among cases than that among controls (11.27%) (p = 0.030). The study found that factors, namely subclinical hypothyroidism, BMI and socioeconomic status to be significantly associated with metabolic syndrome in univariate analysis. After adjustment by binary logistic regression analysis, all these three variables persisted to be significantly associated with metabolic syndrome with risk of having the condition being 2.3(95% CI = 0.9 – 5.8) times higher in subclinical hypothyroidism , 2.3(95% CI = 1.4 – 8.1) times higher in overweight/obese individuals and 2.8(95% CI = 1.3 – 5.8) times more in patients with affluent socioeconomic class (p = 0.038, p = 0.007 and p = 0.006 respectively) than those from their respective counterpart. Diverse reports have suggested that the presence of metabolic syndrome can lead to a higher risk for subclinical hypothyroidism [17]. The largest cohort study conducted on 66,822 participants with and without metabolic syndrome Chang and associates [17], made an average follow-up of 4.2 years to see the incident rates for subclinical hypothyroidism. A study shows that out of the 300 patients, 161 had abnormal thyroid values. Around 54% of the study population had thyroid dysfunction, of which most of them had subclinical hypothyroidism (113 of 300 patients - 37.7%) followed by 43 patients with hypothyroidism (14% of the study population) [18]. The subclinical hypothyroidism was substantially higher in participants who have had metabolic syndrome at the start of study compared with participants who did not have MetS. In contrast, Garduno-Garcia et al determined in more than 3,000 Mexican subjects a lack of association between SCH and MetS risk [19]. In our study 71 cases 49(69.01%) had central obesity (waist circumference > 90 cm for male and > 80 cm for female), 58(81.69%) had raised triglycerides (TG ≥ 150 mg/dl), 62(87.32%) exhibited raised blood pressure (≥ 130/85), 60(84.51%) had hyperglycemia (fasting blood glucose ≥ 100 mg/dl) and only 12(16.90%) had reduced HDL (< 40 mg/dl for male and < 50 mg/dl for female). This study show prevalence of subclinical hypothyroidism was considerably higher among females with metabolic syndrome (31.6%) than that among their male (18.8%), although the difference did not turn to significant (p = 0.221). Cases were relatively older than the controls (p=0.120) and subclinical hypothyroidism is more common in elderly people. Metabolic syndrome appears to be a risk factor for subclinical hypothyroidism. In the context of higher cardiovascular risk associated with subclinical hypothyroidism and the metabolic syndrome, the current analysis suggest that thyroid dysfunction may be one intermediate factor between metabolic syndrome and cardiovascular disease [17]. Subclinical hypothyroidism has clinical importance because of its high prevalence (4–20%), the risk of progression to overt hypothyroidism, and consequences associated with cardiac and lipid abnormalities [20]. A number of studies have reported that subclinical hypothyroidism is associated with an increased risk of coronary heart disease (CHD) and there appears to be a significant increase in a cluster of metabolic CVD risk factors among people with subclinical hypothyroidism [21]. Hueston and Pearson also found that higher percentage of subclinical hypothyroid patients had elevated total cholesterol and LDL cholesterol and decreased HDL compared to control [22]. A study by Terán and Calle also showed that TSH levels have statistically significant association with total

cholesterol and LDL levels but are not a good clinical predictor in this process [23]. Study by Wang et al. however did not report any significant correlation of TSH with CVD risk factors in subclinical hypothyroid patients [25]. In a retrospective study found treatment of subclinical hypothyroidism with levothyroxine was associated with fewer ischemic heart disease events in the younger individuals, supporting a beneficial effect of thyroid hormone on cardiovascular risk factors in hypothyroid patients [25]. Many studies looking at the association of MetS with Thyroid dysfunction and has found more SCH rather than overt hypothyroidism. This study showed that the prevalence of thyroid dysfunction in patients with MetS was 31.84% and its pattern showed high prevalence of SCH (29.32%) followed by hypothyroidism (1.67%) and subclinical hyperthyroidism (0.83%) [26]. This study has found that subclinical hypothyroidism is more common among female patients than male. The prevalence of subclinical thyroid dysfunction among female subjects were higher than those among male subjects in the present study, which is consistent with previous reports. Because subclinical thyroid dysfunction is not rare among the elderly and is more common in women, it is necessary to evaluate the thyroid function among elderly women to identify the possible presence of subclinical thyroid dysfunction [16]. Summarizing the finding of this study, it is evident that there is a strong association between SCH and MetS. The risk of having subclinical hypothyroidism in metabolic syndrome patients was found to be 2.7(95% CI =1.1–6.6) times higher than that in individuals without metabolic syndrome.

VI CONCLUSION

In concluded that subclinical hypothyroidism might be associated metabolic syndrome. Subclinical hypothyroidism demonstrated their significant presence (25.35%) among cases than that among controls (11.27%). The study found that factors, namely subclinical hypothyroidism, BMI and socioeconomic status to be significantly associated with metabolic syndrome in univariate analysis. After adjustment by binary logistic regression analyses, patients of metabolic syndrome carry more than 2.7-fold higher risk of having subclinical hypothyroidism.

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