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Non-lipid risk factors in the development of metabolic syndrome: A case control study

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Abstract

Background: Recently, there has been an interest in identifying non-lipid risk factors in the causation of metabolic syndrome.
Objectives: The present study was aimed to assess the significance of high sensitivity C-reactive protein (hs-CRP)and thyroid profile in patients with metabolic syndrome.
Materials and methods: Patients diagnosed with metabolic syndrome in the outpatient clinic of Department of Medicine were included. Those having ≥3 components of the metabolic syndrome criteria constituted the cases and those with less than three components constituted the controls. Various biochemical parameters were compared between cases and control.
Results: Mean hs-CRP was significantly higher among cases (2.9 ± 0.8mg/L) as compared to controls (1.1 ± 0.7 mg/L), p value <0.05. However, thyroid stimulating hormone (TSH) was not found to be significantly higher among cases as compared to controls (p value >0.5). The clinical thyroid status of the cases was compared against that of control. Among those with metabolic syndrome, overt hypothyroidism was observed in 18.4% and 3% had subclinical hypothyroidism, while among controls, only 4.6% had overt hypothyroidism.
Conclusion: Patients with metabolic syndrome had significantly higher levels of hs-CRP. Though the mean TSH levels were similar, thyroid dysfunction was significantly more common in cases with metabolic syndrome.

Keywords: Metabolic syndrome; risk factors; hs-CRP; Thyroid stimulating hormone

Introduction

Metabolic syndrome is a the constellation of diseases having three or more of the following group of interconnected factors: central adiposity or higher waist circumference, high values of triglycerides, elevated blood pressure, impaired fasting glucose, and decreased high-density lipoprotein (HDL) cholesterol[1]. Many clinical and biochemical parameters are used to risk stratify people at risk of developing metabolic syndrome. Mainly these assessments include are related to lipid profile and body mass index. Recent reports suggest the utility of non-lipid variables in the causation of metabolic syndrome. Systemic inflammation is measured by high sensitivity C-reactive protein (hs-CRP) and it has become an important marker for cardiovascular disease and type 2 diabetes[2]. Moreover hs-CRP is associated with

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the metabolic syndrome and its different components. However, it is not clear whether hs-CRP can also predict the presence of the metabolic syndrome. Likewise, few cross-sectional studies observed that metabolic syndrome and its components are closely related to subclinical hypothyroidism[3]. Despite these known associations, the temporal associations between hypothyroidism and metabolic syndrome remain largely unexplored, though both 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[4]. The present study was aimed to assess the significance of hs-CRP and thyroid profile in patients with metabolic syndrome.

Methodology

Study Design

In the present case control study, patients who were diagnosed with metabolic syndrome in the outpatient clinic of the Department of Medicine, Mamata Medical College, Telangana from January 2019 till December 2019 were included. Metabolic syndrome was diagnose during the 2009 definition which was set by the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; Word Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity, as the presence of three or more of the following five criteria[5]:

- Waist circumference in South Asians >90cm in men and >80cm in women,
- Serum triglycerides levels >150mg/dl,
- Serum HDL cholesterol levels <40mg/dl in men and <50mg/dl in women, under treatment
- Systolic blood pressure >130mmHg and/or diastolic blood pressure >85mmHg) under treatment is an alternate indicator, and
- Fasting serum glucose levels >100mg/dL under treatment
- The same standard is also stated in the modified NECP ATP III definition[6]

The study protocol was approved by the Institutional Ethics Committee. All the participating subjects in the study gave written informed consent.

Sample population

Cases were patients who were diagnosed with metabolic syndrome, as described above. We included cases that had insulin resistance, hypertension, diabetes mellitus, raised waist circumference or BMI. Patients were screened for the presence of the above diagnostic criteria. Those having three or more components of the metabolic syndrome criteria constituted the cases and those with less than three components constituted the controls. We excluded patients with liver or kidney diseases, chronic diseases or recent infections.

Data Collection and Data Analysis

After obtaining approval of the Institutional Ethics Committee, patients were enrolled in the study and data were collected using a case report form. Blood pressure and anthropometric data were measured using standard measurement techniques. Body Mass Index $\geq 23 kg/m^2$was assessed as overweight according to the revised guideline of WHO Western Pacific region.[7]Waist circumference was measured using non-stretchable measuring tape with measurements made halfway between the lower border of the ribs and iliac crest in a horizontal plane. Fasting blood samples were obtained from the. Samples were analysed in an auto-analyser for metabolic syndrome component of fasting plasma glucose, high density lipoprotein and triglycerides. Thyroid profile was done for all patients, for which serum free T3, free T4 and thyroid stimulating hormone (TSH) were measured by using fluorescent immunoassay. High sensitive C-reactive protein (hs-CRP) was assessed by Enzyme Linked

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Immunosorbent Assay (ELISA). The collected data were analysed using Statistical Package of Social Sciences (SPSS) software (version 21). Quantitative data were described as means and standard deviations and qualitative data will be described as frequency distribution. Means were compared using the paired t test for normal data and qualitative data were compared using the chi-square test. A two-sided p-value less than 0.05 were considered statistically significant.

Results

During the study period, we included a total of 65 cases of metabolic syndrome and equal number of age and gender matched controls. Baseline characteristics of the patients have been described in Table 1. Mean age and gender distribution was comparable between the cases and controls. Mean BMI was 26.8 ± 5.3 and 25.9 ± 5.1 kg/m^{2}in the cases and controls respectively, which was statistically similar as well. The proportions of smokers in the two study groups were also similar. However, mean values of fasting blood sugar, triglycerides, systolic blood pressure, diastolic blood pressure and waist circumference were significantly higher among the cases as compared to controls. Mean fasting blood sugar was 149.1 ± 16.4mg/dl in cases and 89.3 ± 5.6mg/dl in controls. Mean triglycerides were measured as 251.9 ± 14.2mg/dl in cases and 142.8 ± 8.3mg/dl in control group. Mean systolic blood pressure was found to be 149.7 ± 5.3mm Hg in cases and 118.4 ± 6.3mm Hg in controls, while mean diastolic blood pressure was 89.3 ± 6.7mm Hg in cases and 74.1 ± 5.9mm Hg in controls.

Table 1. Baseline characteristics of the cases and controls included in the study

Patient variables	With metabolic syndrome (n=65)	Without metabolic syndrome (n=65)	P value
Age (in years)	60.1 ± 6.23	62.3 ± 4.03	NS
Gender (M/F)	33/32	34/31	NS
Body mass index (kg/m^2)	26.8 ± 5.3	25.9 ± 5.1	NS
Smokers (n, %)	32, 50%	33, 51%	NS
Fasting blood sugar (mg/dl)	149.1 ± 16.4	89.3 ± 5.6	< 0.05
Triglycerides (mg/dl)	251.9 ± 14.2	142.8 ± 8.3	< 0.05
Systolic blood pressure (mm Hg)	149.7 ± 5.3	118.4 ± 6.3	< 0.05
Diastolic blood pressure (mm Hg)	89.3 ± 6.7	74.1 ± 5.9	< 0.05
Waist circumference (cm)	97.5 ± 4.5	84.6 ± 5.3	< 0.05

NS: not significant

Non-lipid factors like hs-CRP and TSH were measured in both cases and controls (Table 2). We found the mean hs-CRP to be significantly higher among cases (2.9 ± 0.8mg/L) as compared to controls (1.1 ± 0.7 mg/L), p value <0.05.

Table 2: Comparing mean values of hs-CRPand TSH values among cases and controls

Risk factor variables	With metabolic syndrome (n=65)	Without metabolic syndrome (n=65)	P value
hs-CRP (mg/L)	2.9 ± 0.8	1.1 ± 0.7	<0.05
TSH (μIU/dl)	3.8 ± 0.2	2.9 ± 0.8	NS

However, TSH was not found to be significantly higher among cases as compared to controls (p value >0.5). The clinical thyroid status of the cases was compared against that of controls (Table 3).

Table 3: Comparison of thyroid profile among cases and controls

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Thyroid status	With metabolic syndrome (n=65)	Without metabolic syndrome (n=65)	P value
Hypothyroidism			< 0.01
Overt	12 (18.4%)	3 (4.6%)	
Subclinical	2 (3%)	1 (1.4%)	
Hyperthyroidism			
Overt	5 (7.6%)	0 (0%)	
Subclinical	2 (3%)	2 (3%)	
No thyroiddysfunction	44 (68%)	59 (91%)	

Overall, 32% of the cases of metabolic syndrome had some form of thyroid dysfunction, which was significantly higher than that of controls (9%). Hypothyroidism was the most common thyroid abnormality. Among those with metabolic syndrome, overt hypothyroidism was observed in 18.4% and 3% had subclinical hypothyroidism, while among controls, only 4.6% had overt hypothyroidism and 1.4% had subclinical hypothyroidism.

Discussion

The present study was done to assess the biochemical factors which are associated with metabolic syndrome. We observed that fasting blood sugar levels, serum triglyceride, systolic and diastolic blood pressures were significantly higher in patients with metabolic syndrome as compared to their healthy controls. Patients with metabolic syndrome have significantly higher levels of hs-CRP when compared to controls. Though the mean TSH levels were similar, thyroid dysfunction was significantly more common in cases with metabolic syndrome.

We found that patients diagnosed with metabolic syndrome had significantly higher hs-CRP as compared to controls. Babu *et al*. there was higher mean concentration of hs-CRP in patients with metabolic syndrome and there was a linear increase in the values with increasing number of components of the metabolic syndrome[8].Mahajan *et al*. also had similar results where hs-CRP values were significantly elevated in subjects with metabolic syndrome compared to subjects without metabolic syndrome[9]. This suggests the fact that higher the number of components of metabolic syndrome in a patient, higher the values of hs-CRP and the risk of development of cardiovascular events. In a recent study, Carbone *et al*. reported that low baseline hs-CRP was associated with hypertension remission in patients with metabolic syndrome[10].In their study, patients with low baseline hs-CRP (<2 μg/mL) was associated with hypertension remission, a findings which was independent of anti-hypertensive treatment, baseline systolic blood pressure and waist circumference improvement. Mirhafez *et al*. investigated hs-CRP levels in 3285 patients with metabolic syndrome[11]. They found that the concentration of hs-CRP was elevated with increasing the number of MetS components from 1.08 mg/l to 2.55 mg/l. Moreover, subjects who had increased waist circumference, triglyceride, blood pressure and fasting blood glucose based on a had serum hs-CRP concentrations of 0.53, 0.38, 0.34 and 0.71mg/l, respectively, higher than normal values.

Thyroid profile testing was done for all study participants. It was observed that mean TSH levels were comparable for cases and controls. However, 32% of the cases of metabolic syndrome had some form of thyroid dysfunction, which was significantly higher than that of controls (9%). Hypothyroidism was the most common thyroid abnormality. Although the underlying mechanism is not clearly understood, chronic inflammation and disturbed metabolic state has been observed in patients of metabolic syndrome. These underlying processes enhance the pathogenesis of metabolic syndrome[12].Hyperglycemia and inflammation of metabolic syndrome result in increased production of reactive oxygen species, which in turn increase oxidative stress causing excessive activation of nicotinamide adenine dinucleotide phosphate oxidase[13].Hypermetabolic state in hyperthyroidism may accelerate free radical production in mitochondria and may reduce the antioxidant defence

system. In hypothyroidism, associated oxidative stress is the consequence of reduced capacity of the antioxidative defence.

Deshmukh *et al*. assessed the prevalence and clinical and epidemiological factors of thyroid dysfunction in Indian patients diagnosed with metabolic syndrome. Of the 432 metabolic patients, overt hypothyroidism was reported in 76 (17.59%) patients and overt hyperthyroidism in 7 (1.62%) patients. Subclinical hypothyroidism, overt hypothyroidism, and subclinical hyperthyroidism were reported in 8.10%, 1.60%, and 0.70% patients with newly diagnosed TD, respectively. A similar prevalence of hypothyroidism was reported in patients with metabolic syndrome in other Indian studies as well, like in Meher *et al*. (26%)[14] and Shantha *et al*. (29.3%)[15]. Khatiwada *et al*. assessed thyroid function in metabolic syndrome patients and evaluated its relationship with the components of metabolic syndrome[16].The authors found that thyroid dysfunction was seen in 31.9% (n = 54) metabolic syndrome patients. Subclinical hypothyroidism (26.6%) was the major thyroid dysfunction followed by overt hypothyroidism (3.5%) and subclinical hyperthyroidism (1.7%). In another study, Chang *et al*. found that overt and subclinical hypothyroidism were both significantly associated with metabolic syndrome with OR 1.89 (95% CI: 1.19–2.99) and 1.48 (95% CI: 1.28–1.71) respectively[17].

There are a few limitations of this study. This was a single centre study, which could limit the generalize ability of the results of the present study. Second, a modest sample size was included. Despite these limitations, our case control study design helped in removing selection bias and some confounders. Also non-lipid related risk factors in metabolic syndrome have not been studied in this region of India.

Conclusion

From the results of the present study it can be concluded that, patients with metabolic syndrome have significantly higher levels of hs-CRP when compared to controls. Though the mean TSH levels were similar, thyroid dysfunction was significantly more common in cases with metabolic syndrome. Based on the results of our study, we recommend investigating other non-lipid factors like serum albumin, serum creatinine and serum uric acid in the pathophysiology of metabolic syndrome.

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