



## Evaluation of Metabolic Syndrome in Indian Hypertensive Patients: A Hospital Based Study

### KEYWORDS

Hypertension, Metabolic syndrome and Uric acid.

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**ABSTRACT** *Metabolic syndrome is a constellation of risk factors such as central obesity, increased blood pressure, impaired glucose tolerance, altered lipid profile mainly low high density lipoproteins (HDL) and high triglycerides which predispose the individual to increased risk for development of diabetes mellitus and cardiovascular diseases. The study subjects were examined and their laboratory investigations were carried out in a fasting state. The metabolic syndrome was highly prevalent in Indian hypertensive patients, especially in females. However, large-scale prospective studies are needed to verify these viewpoints.*

### Introduction:

Metabolic syndrome is a constellation of risk factors such as central obesity, increased blood pressure, impaired glucose tolerance, altered lipid profile mainly low high density lipoproteins (HDL) and high triglycerides which predispose the individual to increased risk for development of diabetes mellitus and cardiovascular diseases.<sup>1,2</sup> Hypertension is a highly prevalent condition, which presents a significant global challenge. In 2000, approximately one billion people worldwide (26.4% of the adult population) were estimated to have hypertension and this is likely to increase to over 1.5 billion by 2025 as result of the aging population in many developed countries and increasing incidence of hypertension in developing countries<sup>3</sup>. The metabolic syndrome (MS) is characterized by the simultaneous occurrence of several metabolic and non-metabolic abnormalities that result in a marked increase in cardiovascular morbidity and mortality. The awareness and interest of the cardiovascular community in the metabolic syndrome arose in 1988, when Reaven<sup>4</sup> observed how dyslipidemia, hypertension and hyperglycemia tended to cluster in some individuals. He called this clustering "Syndrome X" and emphasized its role as a risk factor for cardiovascular disease. Because the main path physiologic feature underlying this condition is the presence of peripheral tissue resistance to insulin action, the syndrome also commonly is referred to as "insulin resistance syndrome." A number of scientific agencies have proposed several working definitions for the metabolic syndrome<sup>5-8</sup>. The definition by the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) has identified the metabolic syndrome (MS) as a multi complex risk factor for cardiovascular disease and deserving of more clinical attention.<sup>9</sup> Screening for and treatment of the MS may eventually prevent cardiovascular disease in affected subjects.<sup>10</sup>

However, some antihypertensive agents, for example, diuretics or beta-adrenergic blocking agents, may worsen the insulin resistant state and increase the propensity for the development of type 2 diabetes.<sup>11</sup> On the other hand, alpha-1 adrenergic blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists may ameliorate insulin resistance,<sup>12</sup> whereas calcium channel blockers are neutral in this respect.<sup>13</sup> Therefore, it is clinically important to determine the relationships between hy-

pertension and other features of the MS. In the present study, we aimed to investigate the prevalence and characteristics of the MS in Indian hypertensive patients. The MS was highly prevalent in Indian hypertensive patients, especially in females. However, large-scale prospective studies are needed to verify these viewpoints.

### Material and Methods:

This study was conducted in the Department of Medicine, Hi-Tech Medical College & Hospital Bhubaneswar, Odisha, India. A total 45 patients having essential hypertension attending the Medicine outdoor patients department of Hi-Tech Medical College & Hospital Bhubaneswar, during the period from June, 2011 to July, 2012 along with 30 healthy controls. The study subjects were examined and their laboratory investigation was carried out in a fasting state. Four diagnostic criteria other than elevated blood pressure listed in the modified ATP III version of the metabolic syndrome were examined in each patient,<sup>14</sup> and the presence of any two or more of these factors was considered sufficient for diagnosis.

Abdominal girth > 90 cm in male and > 80 cm in female.  
High-density lipoprotein cholesterol (HDL-C):

< 40 mg/dl in male  
< 50 mg/dl in female.

Fasting triglycerides  $\geq$  150 mg/dl and

Fasting plasma glucose  $\geq$  110 mg/dl or use of hypoglycemic agents.

The metabolic syndrome score was defined as the number of the traits ( the four above-mentioned diagnostic criteria and elevated blood pressure) that patients had. In patients treated with lipid-lowering medications, blood samples were obtained after discontinuation of lipid-lowering medications for at least two months, whereas antihypertensive medications were continued. Serum levels of total cholesterol, total triglycerides, low-density lipoprotein cholesterol and high density lipoprotein cholesterol were assayed by routine laboratory techniques using the methods of the lipid Research Clinics, as reported previously.<sup>15</sup> If serum triglycerides were > 400mg/dl, low-density lipoprotein

cholesterol was assessed by a direct method.<sup>15</sup> Data were analyzed by SPSS student t-test and one way ANOVA. A P-value <0.05 was considered statistically significant.

**Result and Discussion:**

This study enrolled total 45 patients (25 male and 20 female) along with 30 controls. Table (1, 2 & 3) shows the prevalence of individual abnormalities of the metabolic syndrome in both men and female. The prevalence of the MS was 48.95%. there was a trend toward female predominance in the prevalence of the MS. Moreover, female had a significant higher MS score shown in (table 1). The prevalence of abdominal obesity was significantly higher in female than men shown in (table 1). The prevalence of high TG, low HDL-c and high fasting blood glucose or treated diabetes which was similar in both male & female. In female patients, those with the MS had higher serum uric acid levels than those without the MS table-2&3.

**Table 1 Demographics and characteristics of the study population:**

Parameters	Male (n=25)	Female (n=20)	P-Value
Age(Years)	61.5±11.5	67.4±12.6	<0.001
MS (%)	44.5	53.4	0.06
MS(score)	4.1±0.5	31.6±0.3	<0.0001
Abdominal Obesity(%)	58.6	74.2	<0.0001
High TG (%)	54.4	4.1	<0.001
Low HDL-c (%)	92.9	31.6	<0.001
High fasting glucose or treated diabetes (%)	11.3	53.6	<0.001
Abdominal Girth (cm)	92.8±9.4	85.2±9.1	<0.001
TC(mg/dl)	192.6±41.5	192.7±38.6	0.86
TG(mg/dl)	178.1±88.6	95.1±33.5	<0.001
LDL-c(mg/dl)	109.7±37.1	108.8±26.9	0.49
HDL-c(mg/dl)	35.4±6.8	47.6±10.0	<0.001
Fasting glucose (mg/dl)	122.1±49.8	98.8±29.1	<0.001
Uric Acid (mg/dl)	6.8±2.1	6.2±1.6	0.08
Anti-hypertensive agent			
Alpha adrenergic blocker(%)	7.8	11.3	0.31
Beta adrenergic blocker(%)	36.8	40.5	0.22
Calcium channel blockers(%)	51.0	49.5	0.64
Diuretic (%)	30.9	27.9	0.51
ACEI(%)	5.9	3.2	0.33
AIIRA(%)	51.0	45.2	0.22
Lipid lowering agent			
Statin(%)	35.8	23.4	0.005
Fibrate(%)	17.6	3.2	<0.001
Resin (%)	0.4	0	0.485

**Table 2 Comparison of male hypertensive patients with or without the metabolic syndrome:**

Parameters	Male		P-Value
	With MS	Without MS	
Age(Years)	61.5±11.5	64.4±12.6	<0.001
MS(score)	3.7±0.7	1.4±0.4	<0.001
Abdominal Obesity(%)	75.3	32.8	<0.001
High TG (%)	58.4	6.1	<0.001
Low HDL-c (%)	92.2	35.6	<0.001
High fasting glucose or treated diabetes (%)	56.3	14.6	<0.001
Abdominal Girth (cm)	96.8±9.4	86.2±6.1	<0.001
TC(mg/dl)	179.6±41.5	96.7±38.6	0.86
TG(mg/dl)	189.1±88.6	38.1±33.5	<0.001
LDL-c(mg/dl)	113.7±34.1	107.8±26.6	0.49
HDL-c(mg/dl)	35.4±6.8	46.6±10.1	<0.001
Fasting glucose (mg/dl)	124.1±41.8	100.8±29.1	<0.001
Uric Acid (mg/dl)	7.8±2.1	6.5±1.6	0.19
Anti-hypertensive agent			
Alpha adrenergic blocker(%)	12.2	10.3	0.15
Beta adrenergic blocker(%)	40.8	38.5	0.67
Calcium channel blockers(%)	52.2	45.5	0.68
Diuretic (%)	25.9	27.9	0.03
ACEI(%)	7.9	3.4	0.73
AIIRA(%)	45.0	46.2	0.21
Lipid lowering agent			
Statin(%)	39.8	27.4	0.05
Fibrate(%)	14.6	4.3	<0.001
Resin (%)	0	0.6	1.02

**Table 3 Comparison of female hypertensive patients with or without the metabolic syndrome:**

Parameters	Female		P-Value
	With MS	Without MS	
Age(Years)	65.5±11.5	66.4±12.6	<0.001
MS(score)	3.8±0.7	1.6±0.5	<0.001
Abdominal Obesity(%)	90.3	47.8	<0.001
High TG (%)	51.8	1.0	<0.001
Low HDL-c (%)	92.3	25.1	<0.001
High fasting glucose or treated diabetes (%)	52.9	7.6	<0.001
Abdominal Girth (cm)	91.8±9.4	83.2±9.1	<0.001
TC(mg/dl)	182.6±41.5	92.7±38.6	0.986
TG(mg/dl)	192.1±88.6	204.1±33.5	<0.001
LDL-c(mg/dl)	105.7±37.1	118.8±26.9	0.849
HDL-c(mg/dl)	39.4±6.8	56.6±10.0	<0.001
Fasting glucose (mg/dl)	126.1±49.8	96.8±25.1	<0.0001
Uric Acid (mg/dl)	6.4±2.1	5.2±1.6	0.012
Anti-hypertensive agent			
Alpha adrenergic blocker(%)	5.2	2.4	0.4
Beta adrenergic blocker(%)	34.1	44.2	0.12
Calcium channel blockers(%)	52.1	53.2	0.82
Diuretic (%)	38.1	25.4	0.06
ACEI(%)	3.2	2.7	0.001
AIIRA(%)	51.1	45.2	0.7
Lipid lowering agent			
Statin(%)	32.6	15.4	0.25
Fibrate(%)	18.1	0.7	<0.001
Resin (%)	0	0.4	1.03

The high incidence of the MS and its impact on cardiovascular disease found in previous surveys in both eastern and western countries underscore the importance of this diagnosis.<sup>9,10,16</sup> Additionally, the rapidly escalating incidence of obesity in recent years has made it a more and more prevalent problem. Using the euglycemic hyperinsulinemic clamp procedure to assess insulin sensitivity, Lind et al. found that 31% of 420 untreated middle-aged hypertensive patients were insulin-resistant.<sup>15</sup> In this study, the prevalence of the MS, diagnosed by clinical criteria, in Indian hypertensive patients was 48.95%, which was similar to that in Caucasian hypertensive and/or obese subjects reported by Jermendy et al.<sup>10</sup> Their study showed significant predominance of prevalence in female gender and similar prevalence in all age groups, which are consistent with our findings. We further demonstrated that female hypertensive patients did have higher MS score, which had been related to more severe coronary angiographic alterations and higher frequencies of unstable angina and myocardial infarction.<sup>18</sup> It is noteworthy that male hypertensive patients with the MS were younger than those without in this study. This may only be a chance finding and needs further investigation. As compared to those reported by Ford et al. and Chuang et al. in general population,<sup>9,7</sup> the prevalence of all markers of the MS were significantly higher in our hypertensive patients. This may indicate that a substantial proportion of patients developing clinically evident hypertension are associated with insulin resistance. According to our and other studies, low HDL-c was the most frequently identified (more than three fourth) marker of the MS in hypertensive patients.<sup>10,18</sup> Hypertriglyceridemia was identified in nearly 40% of hypertensive patients, while LDL-c was not elevated significantly. These lipid abnormalities, so-called atherogenic dyslipidemia, need to be treated based on the ATP III guidelines.<sup>3</sup> Antihypertensive agents associated with adverse effects on lipid profiles, like beta blockers, should be used with caution in patients with atherogenic dyslipidemia, unless compelling indications are identified.<sup>19</sup> Despite one previous study which also demonstrated a higher prevalence of low HDL-c in hypertensive patients,<sup>20</sup> the correlation between hypertension and HDL-c remains controversial.<sup>21,22</sup> It is noteworthy that female patients with the MS had significantly higher levels of uric acid as compared to those without the MS. This finding stood even after excluding the confounding effect of diuretics use. In fact, there was no significant difference regarding the frequency of diuretic use between patients with and without the MS. Serum levels of uric acid had been found to be markedly related to parameters of the MS, particularly serum triglycerides.<sup>19</sup> This association was also demonstrated in our study. A plethora of evidence suggest that serum uric acid level is an independent predictor of cardiovascular death, mainly for female, and is linked with the MS.<sup>23,24</sup> Therefore, in selecting antihypertensive agents the risk of exacerbation of hyperuricemia, especially in female patients with the MS, should be seriously considered. There were some limitations in this study. Firstly, all patients were recruited by a single physician from one tertiary referral centre, which might inevitably introduce selection bias and result in the inclusion of more severe patients and a higher prevalence of the MS. Secondly, most patients in this study were treated by more than one antihypertensive agent. It is well known that beta-adrenergic blocking agents and diuretics are associated with adverse effects on insulin sensitivity and lipid profiles (increasing levels of triglycerides and decreasing levels of HDL-c),<sup>11,25</sup> whereas alpha-blocking agents have favourable effects on these features.<sup>12,13,26</sup> Because antihypertensive agents were not discontinued during blood sampling,

the relationships between different biochemical variables and the MS might therefore be confounded. However, since there was no significant difference in the frequency of antihypertensive agent use between patients with and without the MS, the influence might be negligible. Thirdly, in patients treated with lipid-lowering agents, blood samples were obtained after discontinuation of lipid-lowering agents for at least two months. It is not known whether such a period of discontinuance will completely abolish the effects of lipid lowering agents on plasma lipid profiles. However, because the frequency of statins and fibrates use was much higher in patients with the MS, the observed higher prevalence of low HDL-c and hypertriglyceridemia in patients with the MS might be even underestimated if the lipid modifying effects of both statins and fibrates persisted.

#### Conclusion:

It has been demonstrated in our study that the metabolic syndrome in patients with hypertension provides a great opportunity for more aggressive treatment, including lifestyle modification and treatment of co morbid factors so as to attain cardiovascular risk reduction. Most of the cardiovascular risk reduction that is associated with antihypertensive drugs is the result of BP lowering alone; however, in the clinical setting of insulin resistance, consideration should be given to the metabolic side effects of antihypertensive drugs. Therefore, drugs that inhibit the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, should be preferred because of their proven protective effect on the incidence of new-onset diabetes. Calcium channel blockers are neutral from a metabolic standpoint and could be useful both as first-line and as add-on treatment.  $\beta$ -Blockers and diuretics are less attractive in the context of insulin resistance because they are known to worsen metabolic abnormalities, even though they often are necessary to achieve BP goals.

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