

## Metabolic Syndrome as a Cardiovascular Risk Factor: A Reality or Just a Multiplex of Risk Factors? A Study on Association Between Endothelial Dysfunction And Metabolic Syndrome as a Cardiovascular Risk Factor

Mani Prasad Gautam,<sup>1\*</sup> Samir Gautam,<sup>2</sup> Subramanyam Gangapatnam,<sup>3</sup> Sogunuru Guruprasad<sup>3</sup>

<sup>1</sup>Department of Medicine, Bharatpur Hospital, Chitwan, <sup>2</sup>Gautam Buddha Hospital, Butwal, Nepal, <sup>3</sup>Department of Cardiology, College of Medical Sciences, Bharatpur, Nepal.

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### Correspondence:

\*Dr. Mani Prasad Gautam,  
Department of Medicine, Bharatpur Hospital, Chitwan, Nepal.  
Email: manigautam@gmail.com  
Phone: +977-9851076043

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### ABSTRACT

**Background:** Metabolic syndrome is a constellation of various cardiovascular risk factors with a potential to double the risk of coronary artery disease. However, in real world scenario, this is just a combination of multiple CV risk factors and its separate existence is somehow regarded as a myth in endothelial function assessment. Endothelial dysfunction is regarded as a precursor and a surrogate marker of atherosclerosis and coronary artery disease. Therefore a study was designed to evaluate the role of metabolic syndrome as a cardiovascular risk factor by assessing endothelial function in subjects with it.

**Methods:** One hundred subjects with various cardiovascular risk factors were selected and endothelial dysfunction was assessed by measuring flow-mediated dilation of brachial artery. The rates of endothelial dysfunction was compared between subjects with and without metabolic syndrome. Similarly the rates of metabolic syndrome was calculated in subjects with and without endothelial dysfunction in this cohorts of cardiovascular risk factors.

**Results:** Out of 100 subjects with cardiovascular risk factors, mean age 46.75 (9.95) years and mean number of risk factors 2.81 (1.17), similarly, there was no significant difference in the rates of metabolic syndrome among subjects with and without endothelial dysfunction (84.85% vs 79.10% respectively;  $p=0.67$ ). Only age and hypertension were associated with endothelial dysfunction.

**Conclusion:** The association between metabolic syndrome and endothelial dysfunction was not significantly different than the association between multiplex of risk factors and endothelial dysfunction. Therefore its putative role as a separate cardiovascular risk factors, rather than just a multiplex still remains under scrutiny if not a myth. Further well-designed study should be conducted to establish the role of metabolic syndrome as a separate cardiovascular risk factor other than just a multiplex.

**Keywords:** metabolic syndrome; endothelial dysfunction; cardiovascular risk factor; flow-mediated dilatation .

### INTRODUCTION

Metabolic syndrome (MS) is a multiplex of interrelated cardiovascular (CV) disease risk factors that increase the likelihood of developing cardiovascular diseases (CVD). The National Cholesterol Education Program's Adult Treatment Panel III (ATP III) report identified the metabolic syndrome as a risk factor for cardiovascular disease.<sup>1</sup> This risk factor constellation and its association with insulin resistance was named as a separate pathophysiological condition; the "metabolic"<sup>1,2</sup> or "insulin resistance"<sup>3</sup> syndrome. This concept was unified and extended with a publication of Reaven's 1988 Banting Medal award lecture.<sup>4</sup> Reaven postulated that the insulin resistance and its compensatory hyperinsulinemia predisposed patients to hypertension, hyperlipidemia, and diabetes and thus was the underlying cause of much CVD. Obesity was not the part of the primary list of disorders caused

by insulin resistance, as proposed by Reaven, but he acknowledged that the obesity was associated with insulin resistance and the management for what he termed "syndrome X" now often called metabolic syndrome was weight reduction and physical activity. The components of metabolic syndrome have a detrimental role in smooth functioning of endothelium. The endothelium is the thin layer of cells that lines the luminal surface of blood vessels, and it plays a critical role in regulating vascular tone, blood flow, and inflammation. Endothelial function is thought to be an important factor in the pathogenesis of atherosclerosis.<sup>5</sup> Dysfunction of the endothelium can lead to the development of atherosclerosis, hypertension, and insulin resistance. Endothelial dysfunction (ED) is both an early marker of vascular disease and a precursor in the development of atherosclerosis.<sup>6,7</sup> Studies have shown that the presence of endothe-

lial dysfunction identifies individuals at increased risk for cardiovascular disease events.<sup>8-11</sup> Major CHD risk factors are associated with endothelial dysfunction which can be diagnosed preclinically.<sup>12</sup> ED as defined by a lower FMD value, has been found to be associated with cardiovascular events.<sup>13</sup> The brachial-artery flow-mediated dilation (FMD) has been extensively used to identify the ED proposed as a surrogate marker of cardiovascular disease.<sup>14-16</sup> The metabolic syndrome (MS) has been regarded as a coronary heart disease (CHD) risk factor (doubles the risk of CHD).<sup>17,18</sup> However, controversy exists regarding the clinical value of the recognition of MS as a distinct entity.<sup>19,20</sup> Similarly, its contribution to CHD in the presence of other major CHD risk factors is largely unknown.<sup>21,22</sup>

## METHODS

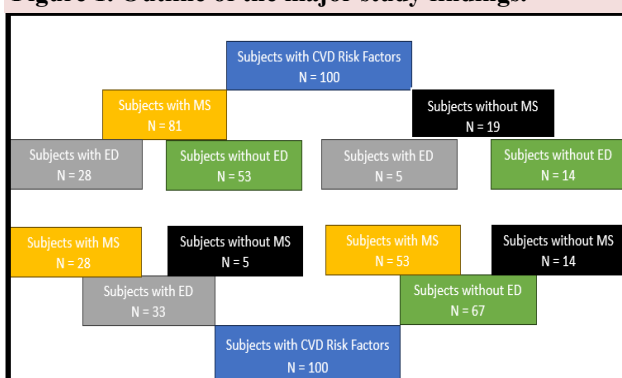
This study was designed to assess the endothelial function in subjects with metabolic syndrome in a cohort of subjects with CHD risk factors. Data was taken from a study which was conducted in 2013 in college of medical sciences, Bharatpur and primarily was designed to study endothelial function in CVD risk factor subjects.<sup>23</sup> The cohort consisted of 100 subjects with at least one out of six major CHD risk factors; Hypertension, Diabetes, Obesity, Age, Dyslipidemia and Smoking. Demographic data and data on CVD risk factors were noted and their endothelial function study data were collected. The subjects were grouped as subjects with and without metabolic syndrome as per the standard definition<sup>1,19</sup>. MS was defined using the revised Adult Treatment Panel III criteria modified for Asian subjects. The ATP III/AHA/NHLB-defined metabolic syndrome required three or more of the following five criteria:<sup>1,19</sup> Waist circumference  $\geq 90$  cm in men,  $\geq 80$  cm in women, Triglycerides  $\geq 150$  mg/dl, or on medicine, High-density lipoprotein (HDL) cholesterol ( $< 40$  mg/dL in men,  $< 50$  mg/dl in women), or on medicine, Fasting plasma glucose concentration  $\geq 100$  mg/dL, or on medicine for hyperglycemia, Blood pressure  $\geq 130/85$  mmHg or on medicine. The details of brachial artery flow-mediated dilation (FMD) report which was measured during by using high-resolution ultrasound vascular probe was copied and used for this study purpose. The details on methodology followed and interpretation of FMD are described in the guidelines given by the International Brachial Artery Reactivity Task Force.<sup>15</sup> ED was defined as FMD  $< 7.35\%$  (lower 3<sup>rd</sup> quartiles). Various variables including the incidenc-

es of endothelial dysfunction among subjects with and without metabolic syndrome were compared. Similarly various variables including the prevalence of metabolic syndrome among these subjects with and without ED were also compared. Quantitative data were reported as means with standard deviation and statistical significance was assessed by using student t test. Qualitative data were reported in percentages and their significance was assessed by using Chi square test. Statistical significance of differences were established on the basis of p values; p less than 0.05 was taken as statistically significant value.

## RESULTS

A total of 100 subjects with CHD risk factors were included in the study. Mean age was 46.75 (9.95) years, 42% subjects were males and mean numbers of CHD risk factors in one individual was 2.81 (1.17).

**Figure 1. Outline of the major study findings.**



The major study findings are shown in figure 1. Out of 100 subjects, 81 subjects met the criteria for MS and among 81 MS subjects, 28 subjects had ED and remaining had normal endothelial function. Among 19 non-MS subjects, 5 had ED and 14 had normal endothelial function. The difference in the prevalence of ED among MS and non-MS subjects was non-significant ( $p = 0.67$ ). On the other hand, out

**Table 1. Comparison of various parameters in subjects with and without metabolic syndrome.**

Parameters	Subjects with MS	Subjects without MS	P value
Age (Years)	46.2 $\pm$ 9.87	49.11 $\pm$ 10.18	0.93
Male	29 (35.8)	13 (68.42)	0.02
Change in BAD (mm)	0.36 $\pm$ 0.17	0.41 $\pm$ 0.2	0.32
FMD	9.69 $\pm$ 4.75	10.65 $\pm$ 4.82	0.43
Endothelial dysfunction (%)	28 (34.57)	5 (26.32)	0.67
Number of CHD risk factors	2.91 $\pm$ 1.21	2.36 $\pm$ 0.9	0.06

**Table 2. Comparison of various parameters in subjects with and without endothelial dysfunction.**

Parameters	Subjects with ED (n=33)	Subjects without ED (n=67)	p Value
Mean Age (yrs)	51.87± 8.57	44.22± 9.64	0.0002
Male (%)	19 (57.58)	23 (34.33)	0.04
Mean increase in BAD (mm)	0.17± 0.11	0.46± 0.11	NA
Mean FMD	4.36±2.23	12.59±2.97	NA
Mean number of risk factors	3.67± 1.08	2.38± 0.97	0.0003
Major CHD Risk factors (%)			
i. Diabetes	6 (18.18)	6 (8.96)	0.3
ii. Hypertension	29 (87.88)	36 (53.73)	0.001
iii. BMI of High Risk	23 (69.7)	40 (59.7)	0.47
iv. Dyslipidemia	30 (90.9)	49 (73.13)	0.07
v. Age (Men ≥ 45, Women ≥ 55)	23 (69.7)	21 (31.34)	0.006
vi. Smoking	10 (30.3)	9 (13.43)	0.07
Metabolic Syndrome	28 (84.85)	53 (79.10)	0.67

of 100 study subjects, 33 subjects had ED and among 33 subjects, 28 subjects met MS criteria and 5 did not. Among 67 subjects with normal endothelial function, 53 met MS criteria and 14 did not. The difference in the metabolic syndrome among subjects with and without ED was also non-significant ( $p = 0.67$ ). When compared between the subjects with and without metabolic syndrome, the

**Table 3. Interrelation between metabolic syndrome and endothelial dysfunction.**

Parameter	ED Present(33)	ED Absent(67)
MS	28 (84.85%)	53 (79.1%)
Non- MS	5 (15.15%)	14 (20.9%)

Parameter	MS(81)	Non-MS(19)
ED Present (33)	28 (34.57%)	5 (26.32%)
ED Absent (67)	53 (65.43%)	14 (73.68%)

parameters; changes in brachial artery dimensions and flow mediated dimensions were 0.36(0.17) vs 0.41 (0.2) mm and 9.69 (4.75) vs 10.65 (4.82) mm respectively. The differences were not significant ( $p = 0.32$  and  $0.43$  respectively). The subjects with endothelial dysfunction were older, 51.87 (8.57) vs 44.22 (9.64),  $p = 0.0002$  and male sex 57.88% vs 34.33%,  $p = 0.04$ , when compared to subjects with normal endothelial function. The subjects with endothelial dysfunction had higher number of CVD risk factors, 3.67(1.08) vs 2.38(0.97),  $p = 0.0003$ . Among various CVD risk factors, hypertension and age were associated with endothelial dysfunction,  $p = 0.001$  and  $p = 0.006$  respectively. The prevalence of metabolic syndrome among subjects with and without endothelial dysfunction were 84.85% and 79.10%,  $p = 0.67$ . Table 3 summarizes the major findings; metabolic syndrome was evident in 79.1% and 84.85% subjects with normal and abnormal endothelial response respectively. ( $p=0.67$ ). In addition, 34.57% and 26.32% subjects with and without MS had ED respectively ( $p = 0.67$ ).

## DISCUSSION

Our study showed that the prevalence of endothelial dysfunction in subjects with metabolic syndrome and in subjects with other multiple CV risk factors were similar. That means, the grouping of certain CV risk factors under the umbrella of metabolic syndrome did not provide any additional meaning except just the constellation of multiple CV risk factors. The risk for atherosclerotic cardiovascular disease as judged by the presence of endothelial dysfunction in these subjects were similar to in those subjects with multiple CV risk factors. There was no difference in the prevalence of endothelial dysfunction (a precursor, a surrogate marker and also a risk factor for atherosclerotic CVD) in subjects with and without metabolic syndrome was similar when examined in the subjects with CV risk factors. Metabolic syndrome has been a controversial topic in the medical community for many years.<sup>21,22</sup> Some experts argue that it is a genuine health condition that affects millions of people worldwide, might lead to various atherosclerotic cardiovascular diseases (ACVD)<sup>17,18</sup> while others believe that it is merely a fiction, a multiplex of various cardiovascular risk factors, falsely extrapolated as a separate disease entity.<sup>19,20</sup> Despite the ongoing debate, there is growing evidence to support the existence of metabolic syndrome. According to the National Institutes of Health, metabolic syndrome is a cluster of medical conditions that include multiple CVD risk factors such as high blood pressure, elevated blood sugar, abnormal cholesterol levels, and excess body fat.<sup>1,19</sup> These conditions often occur together and increase the risk of heart disease, stroke, and type 2 diabetes.<sup>17,18</sup> Research has shown that metabolic syndrome is prevalent in both developed and developing coun-

tries, affecting up to one-fourth of the adult population worldwide.<sup>24</sup> In addition, studies have demonstrated that individuals with metabolic syndrome are at increased risk of cardiovascular events compared to those without the condition. Critics of metabolic syndrome argue that it is merely a collection of risk factors that do not necessarily indicate a specific disease.<sup>19-22</sup> However, proponents of the syndrome counter that it serves as a useful tool for identifying individuals at increased risk of developing serious health problems and for implementing preventative measures. Our study was unable to show any significant association between endothelial dysfunction and metabolic syndrome when compared with the subjects having CVD risk factors. The prevalence was similar in subjects with multiple CVD risk factors and metabolic syndrome. Interestingly, our study also proves that metabolic syndrome is just a multiplex of CVD risk factors or non-inferior to multiple CVD risk factors when judged by the presence of endothelial dysfunction. Studies have shown that both the metabolic syndrome and endothelial dysfunction are risk factors and provide additive prognostic values in predicting cardiovascular events.<sup>10</sup> Our study also showed more than one third of the MS subjects had endothelial dysfunction, but its prevalence was similar in subjects with multiple CVD risk factors but without metabolic syndrome and in subjects with metabolic syndrome. Wei et al had studied the association between metabolic syndrome and endothelial dysfunction in adolescents by using von Willebrand factor (vWF) and plasminogen activator inhibitor-1 (PAI-1) as biomarkers of endothelial dysfunction.<sup>25</sup> These biomarkers were significantly increased in subjects with metabolic syndrome when compared with healthy controls and correlated with obesity, dyslipidemia, raised blood sugar and hypertension. But similar study by Mimoun et al in obese children, where endothelial function was assessed by non-invasive ultrasound measurement of intima-media thickness was not able to prove the association with metabolic syndrome.<sup>26</sup> Although some of the individual clinical features that make up the syndrome are predictive of clinical outcomes, but whether the grouping these features together under the umbrella of MS adds additional diagnostic, therapeutic, and prognostic value remains the subject of ongoing debate.<sup>21,22</sup> Moreover, neither population showed a relationship between CV outcomes and three of the MS criteria (for waist circumference, TG, Glucose >100).<sup>27,28</sup>

Our study did show the higher incidence of ED with the presence of multiple CHD risk factors, but that association with MS was not significant statistically when compared with the subjects with multiple CVD risk factors. It is likely that the extra CV risk associated with the MS is merely the additive of multiple CHD risk factors. From this current study, it is likely that the association of endothelial dysfunction and metabolic syndrome is comparable to the association of endothelial dysfunction and multiple CV risk factors. On another side, it shows that metabolic syndrome is equivalent to multiplex of CV risk factors, it is neither superior nor inferior to it.

## CONCLUSION

Based on our observation we conclude that the association between metabolic syndrome and endothelial dysfunction was not superior to the association between multiple CVD risk factors and endothelial dysfunction. Therefore, its putative role as a separate cardiovascular risk factor other than just a multiplex of risk factors still remains under scrutiny if not a myth. Albeit, it is not inferior to multiple CVD risk factors. Further well-designed study should be conducted to establish its role as a strong cardiovascular risk factor and the findings should be compared with healthy matched controls. Among conventional CV risk factors hypertension was the only cardiovascular risk factor associated with endothelial dysfunction in both univariate and multivariate analysis. While the debate over the reality of metabolic syndrome continues, the evidence suggests that it is a legitimate health condition that warrants attention from medical professionals and it is non-inferior to multiple CVD risk factors. Further research is needed to better understand the causes and underlying mechanisms of the syndrome as a separate clinical entity, as well as effective prevention and treatment strategies

## Limitations

This Study was designed to assess the association between metabolic syndrome and endothelial dysfunction. But all the subjects in this study had one or more major CVD risk factors and comparison was made with the subjects having other CVD risk factors. So, making a conclusion that metabolic syndrome is not associated with endothelial dysfunction will become erratic and irrational. It can only conclude that metabolic syndrome was equivalent to multiple risk factors in term of CVD risks



and endothelial dysfunction; a precursor of atherosclerosis and related CVD. Its descriptive nature, cross-sectional design and small sample size are the major limitations. Similarly, the data comparison between metabolic syndrome subjects and subjects with multiple CVD risk factors should be taken seriously while deriving any conclusions and extrapolating it in general.

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**Conflict of Interest:** None.

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