

# **ASSOCIATION OF INFLAMMATORY MARKERS WITH METABOLIC SYNDROME AMONG PRE & POST- MENOPAUSAL WOMEN**

## **ABSTRACT**

**Background:** Metabolic Syndrome (MetS) comprises of an array of clinical, physiological, metabolic and biochemical disturbances; associated with a systemic inflammatory response. The debilitating condition entails high morbidity and mortality and thus it is important to identify and resolve it timely; a goal which may be achieved with the help of biomarkers. Fibrinogen and hsCRP; highly sensitive C-reactive protein, are found to be increased in acute inflammations. The raised quantity is indicative of underlying inflammatory states and thus may be relevant to MetS.

**Objectives:** To determine the association of inflammatory markers with metabolic syndrome among pre & post-menopausal women.

**Materials & Methods:** This cross-sectional analysis was carried out on a sample of 278 women (aged at or above 25 years) presenting to the Outpatient Department of General Medicine and the Obstetrics – Gynecology at Liaquat University Hospital (Hyderabad) from 01-02-2020 to 01-10-2020. Data was collected using a structured interview-based proforma which include information

about biodata and sociodemographic details of research participants and biochemical analysis (CRP, DLC and fibrinogen and insulin measurement).

**Results:** In this study a cumulative MetS prevalence was found out to be around 60% (63.7% as per IDF criteria and (57.6% as per ATP-III classifications). Women with MetS had higher levels of CRP and fibrinogen. Women with high fibrinogen levels and CRP suffered with more type of metabolic abnormalities.

**Conclusion:** The findings of this studies showed that with total body fat and fat percentage, body mass-index, have a positive association with the studied inflammatory markers (CRP and fibrinogen).

**Keywords:** Metabolic Syndrome, Inflammatory Marker, CRP, fibrinogen.

## INTRODUCTION

Metabolic syndrome is a cluster of clinical, physiological, metabolic, and biochemical features that are strongly related with an enhanced risk of occurrence of Type 2 diabetes mellitus and cardiovascular diseases and atherothrombotic complications.<sup>1, 2</sup> Metabolic syndrome leads to hormone resistance that alters normal endocrine function. Leptin resistance in these patients leads to ineffective appetite suppression and thus allows accumulation of excessive calories as visceral fat. Moreover, increased number of fat cells leads to increased production of adipokines that causes chronic inflammation. This inflammation forms the basis of several concurrent manifestations.<sup>3, 4</sup>

It has been widely reported that cellular oxidative stress and sustained inflammatory state of the body are cornerstones in developments and deterioration of many clinical conditions, including those that occur concurrently with MetS (such as atherosclerotic vascular disease and obesity).<sup>5</sup> <sup>6</sup> Increased BMI is found to be linked with raised levels of inflammatory markers in the body<sup>7</sup>, and the later, is also independently reported to be connected with metabolic syndrome which often accompanies obesity.<sup>8</sup>

MetS is related with the inflammatory condition of body, during which central obesity around the viscera occurs. Inflammatory cytokines like IL-1, TNF, and IL-6, persuade the acute phase response of inflammatory process. IL-6, being part of promoter area of C-reactive protein and fibrinogen gene, plays the crucial role in increasing these acute phase proteins.<sup>9,10</sup>

A number of studies substantiated the association of elevated CRP levels in patients with metabolic syndrome.<sup>11 - 15</sup> CRP levels are not only found to be significantly connected with insulin resistance as per the HOMA model but the elevated levels are also found in patients with hypertension, and dyslipidemia.<sup>14</sup> A strong unidirectional association is present among elevated levels of hsCRP, insulin resistance and central visceral adiposity<sup>16 - 20</sup>

Due to a number of studies reported in literature about the association of increased hsCRP and the development of MetS<sup>11, 12</sup>, we designed the study to find out if there is any association, present among the inflammatory markers in pre-menopausal and post-menopausal women having metabolic syndrome.

## **OBJECTIVES**

To determine the association of inflammatory markers with metabolic syndrome among pre & post-menopausal women.

## **METHODOLOGY**

This comparative analysis was conducted up on a sample of 278 (147 premenopausal & 131 postmenopausal) women (aged at or above 25 years) presenting to the Outpatient Department of General Medicine and the Obstetrics – Gynecology at Liaquat University Hospital (Hyderabad) from 01-02-2020 to 01-10-2020. Data was collected using a structured interview-based proforma which include information about biodata and sociodemographic details of research participants and biochemical analysis (CRP, DLC and fibrinogen and insulin measurement). All anthropometric measurements along with visceral & body fat level were calculated using measuring tape & OMRON BfF508. SPSS v. 21.0 was used to analyzed data. .

### Inclusion criteria

1. Consenting individuals
2. Aged 25 years and above

#### Exclusion Criteria

1. Women on hormone replacement therapy
2. Pregnant or lactating women
3. Women suffering from secondary hypertension
4. Women with artificial/induced menopause
5. Women taking oral contraceptives
6. Women taking any medicine for HTN, DM, or endocrinological disorders.

#### **Statistical Analysis**

Data was collected and recorded in excel software and then transferred and analyzed (SPSS, version 23 for analysis). Chi square test was applied to check difference of variables between groups. Levene's test was used for homogeneity of variance. The results were said to be significant if the p-value was <0.05.

#### **RESULTS**

Total 278 participants were selected. In this study a cumulative MetS prevalence was found out to be 63.7% and 57.6% according to IDF (WC80 diagnostic criteria) and NCEP ATP-III classifications, respectively. Differences among women with MetS from those without MetS on various important aspects, are tabulated below.

Table 1: Differences among women with MetS from those without MetS

<b>Variables</b>	<b>With MetS n= 160</b>	<b>Without MetS n= 118</b>	<b>P-value</b>
<b>Age (years)</b>	<i>45.50 ± 9.91</i>	<i>38.80 ± 10.07</i>	<i>&lt; 0.01</i>
<b>WC (cm)</b>	<i>99.26 ± 9.39</i>	<i>87.69 ± 9.29</i>	<i>&lt; 0.01</i>
<b>BMI (kg/m<sup>2</sup>)</b>	<i>31.79 ± 4.11</i>	<i>26.58 ± 4.26</i>	<i>&lt; 0.01</i>

<b>WHR</b>	$0.91 \pm 0.05$	$0.88 \pm 0.04$	$< 0.01$
<b>Body fat (%)</b>	$43.79 \pm 6.72$	$34.98 \pm 8.25$	$< 0.01$
<b>Visceral fat</b>	$8.91 \pm 1.75$	$6.83 \pm 1.52$	$< 0.01$
<b>HDL (mg/dl)</b>	$42.31 \pm 9.46$	$48.20 \pm 8.64$	$< 0.01$
<b>LDL (mg/dl)</b>	$131.44 \pm 38.32$	$107.03 \pm 29.80$	$< 0.01$
<b>Triglycerides (mg/dl)</b>	$195.10 \pm 63.37$	$124.7 \pm 44.04$	$< 0.01$

Table 2: Inflammatory markers:

<b>Variables</b>	<b>With MetS n= 160</b>	<b>Without MetS n= 118</b>	<b>P-value</b>
<b>CRP Level (Mean)</b>	$4.07 \pm 1.72$	$2.09 \pm 0.98$	0.0006
<b>Fibrinogen Level (Mean)</b>	$336 \pm 77$	$193 \pm 43$	$< 0.001$

CRP level of 2.6 mg/L predicted the MetS with sensitivity, specificity and accuracy of 71%, 78% and 75% respectively.

## DISCUSSION

In this study, the prevalence of MetS was found to be 59.9%. According to literature review the highest prevalence of MetS in Asian countries was found in urban Pakistan (49.0%).<sup>21</sup> Another study conducted in India showed prevalence of MetS to be 47.2% in female population.<sup>22</sup> yet another study conducted in the urbanized areas of Karachi,<sup>23</sup> showed the prevalence of METS at 34% and 49% according to IDF and NCEP ATP III criteria, the same study shows significantly higher prevalence in old female subjects, that coincides with this study.

Our study shows higher prevalence of METS than another study<sup>24</sup> piloted in Pakistan that showed that the prevalence of METS to be around 57% in females. Our study partially reported the same results as of Gupta *et al.*<sup>25</sup> in which the most commonly element found was persistently elevated blood pressure (51%). Hip to waist ratio (34%) and serum triglycerides (33%) were

other prevalent factors, followed by the diabetes mellitus (17%). Our research on the other hand showcased all variables to be significant with the most markedly including the aforementioned and BMI, LDL and HDL (among others).

Patients with MetS were having much higher level of CRP and fibrinogen than their counterparts. The finding is in line with the studies of Tarantino G et al & Kraja AT et al, who regarded metabolic syndrome as a pro-inflammatory state.<sup>26, 27</sup> Hansel B et al. & Dandona et al. reported a significantly elevated levels of C-reactive protein and fibrinogen in metabolic syndrome in male gender<sup>5, 6</sup> while one other study reported a higher CRP levels in women<sup>28</sup>. Both of these studies are much against the findings of our study. Our studied showed no difference in inflammatory markers between different sexes,

This study reported a positive relation of both inflammatory markers with total body fat and fat percentage, Body mass-index, serum cholesterol, LDL and insulin resistance. Vikram et al.<sup>29</sup> reported observations in line with our findings but he reported an absence of relation between CRP and various lipid parameters in Indian population. Findings opposite to our study have been reported in studies conducted in Japan<sup>30</sup> and China<sup>19</sup>. Raised blood pressure and WHR were in positive relation with inflammatory markers in metabolic syndrome.

## **Conclusion**

The findings of this studies showed that body mass index, body fat mass, percent body fat have a positive association with the studied inflammatory markers (CRP and fibrinogen).

## **REFERENCES**

1. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. *Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Therapeutic advances in cardiovascular disease.* 2017;11(8):215-25.
2. Kaur J. *A comprehensive review on metabolic syndrome. Cardiology research and practice.* 2014;2014:943162.
3. Gade W, Schmit J, Collins M, Gade J. *Beyond obesity: the diagnosis and pathophysiology of metabolic syndrome. Clinical laboratory science : journal of the American Society for Medical Technology.* 2010;23(1):51-61; quiz 2-5.

4. Sharma S, Aggarwal N, Joshi B, Suri V, Badada S. Prevalence of metabolic syndrome in pre- and post-menopausal women: A prospective study from apex institute of North India. *J Mid-life Health* 2016; 7:169-74.
5. Hansel B, Giral P, Nobecourt E, Chantepie S, Bruckert E, Chapman MJ, et al. Metabolic syndrome is associated with elevated oxidative stress and dysfunctional dense high-density lipoprotein particles displaying impaired antioxidative activity. *J Clin Endocrinol Metab.* 2004;89:4963–71.
6. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: A comprehensive perspective based on interactions between obesity, diabetes and inflammation. *Circulation.* 2005;111:1448–54.
7. Festa A, D'Agostino Jr R, Williams K, Karter AJ, Mayer-Davis EJ, Tracy RP, et al. The relation of body fat mass and distribution to markers of chronic inflammation. *Int J Obes Relat Metab Disord.* 2001;25:1407–15.
8. Yajnik CS, Joglekar CV, Lubree HG, Rege SS, Naik SS, Bhat DS, et al. Adiposity, inflammation and hyperglycaemia in rural and urban Indian men: Coronary Risk of Insulin Sensitivity in Indian Subjects (CRISIS) Study. *Diabetologia.* 2008;51:39–46.
9. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis.* 2000;148:209–14.
10. Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE. Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. *Obes Res.* 2001;9:414–7.
11. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14719 initially healthy American women. *Circulation.* 2003;107:391–7.
12. Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Chambless LE, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Arch Intern Med.* 2005;165:2479–84.
13. Sugiura K, Tamakoshi K, Yatsuya H, Otsuka R, Wada K, Matsushita K, et al. Contribution of adipocytokines to low-grade inflammatory state as expressed by circulating C-reactive protein in Japanese men: comparison of leptin and adiponectin. *Int J Cardiol.* 2008;130:159–64.
14. Festa A, D'Agostino Jr R, Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation.* 2000;102:42–7.
15. Vu JD, Vu JB, Pio JR, Malik S, Franklin SS, Chen RS, et al. Impact of C-reactive protein on the likelihood of peripheral arterial disease in United States adults with the metabolic syndrome, diabetes mellitus, and preexisting cardiovascular disease. *Am J Cardiol.* 2005;96:655–8.
16. Gokulakrishnan K, Deepa R, Sampathkumar R, Balasubramanyam M, Mohan V. Association of leukocyte count and hsCRP with metabolic abnormalities in subjects with normal glucose

tolerance (CURES - 64). *J Assoc Phys India*. 2009;57:27–32.

17. Huffman FG, Gomez GP, Zarini GG. Metabolic syndrome and high- sensitivity C-reactive protein in Cubans. *Ethn Dis*. 2009;19:115–20.
18. Ebrahimi A, Nabipour I, Vahdat K, Jafari SM, Fouladvand M, Assadi M, et al. High sensitivity C-reactive protein is associated with the metabolic syndrome independent to viral and bacterial pathogen burden. *Diabetes Res Clin Pract*. 2009;84:296–302.
19. Wen J, Liang Y, Wang F, Sun L, Guo Y, Duan X, et al. Association of C-reactive protein and metabolic syndrome in a rural Chinese population. *Clin Biochem*. 2009;42:976–83.
20. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation*. 2004;109:2818–25.
21. Iqbal Hydrie MZ, Shera AS, Fawwad A, Basit A, Hussain D Sc A. Prevalence of metabolic syndrome in urban Pakistan (Karachi): comparison of newly proposed International Diabetes Federation and modified Adult Treatment Panel III criteria. *Metabolic syndrome and related disorders*. 2009;7(2):119-24.
22. Jafar TH, Qadri Z, Chaturvedi N. Coronary artery disease epidemic in Pakistan-more electrocardiographic evidence of ischemia in women than in men. *Heart*. 2007;94(4):408-413.
23. Ashraf SMS, Ziauddin F, Jahangeer U. Metabolic syndrome in type-2 diabetes mellitus. *Pak J Med Sci* 2006;22:295–299.
24. Ainy E, Mirmiran P, Asl SZ, Azizi F. Prevalence of metabolic syndrome during menopausal transition Tehranian women: Tehran Lipid and Glucose Study (TLGS). *Maturitas*. 2007;58(2):150-5.
25. Gupta R, Sarna M, Thanvi J, Rastogi P, Kaul V, Gupta VP. High prevalence of multiple coronary risk factors in Punjabi Bhatia community: Jaipur Heart Watch-3. *Indian Heart J*. 2004;56:646–52
26. Tarantino G, Marra M, Contaldo F, Pasanisi F. Basal metabolic rate in morbidly obese patients with non-alcoholic fatty liver disease. *Clin Invest Med*. 2008;31:E24–9.
27. Kraja AT, Province MA, Arnett D, Wagenknecht L, Tang W, Hopkins PN, et al. Do inflammation and procoagulation bio- markers contribute to the metabolic syndrome cluster? *Nutr Metab (Lond)*. 2007;4:28–34.
28. Saltevo J, Vanhala M, Kautiainen H, Kumpusalo E, Laakso M. Gender differences in C-reactive protein, interleukin-1 receptor antagonist and adiponectin levels in the metabolic syndrome: a population-based study. *Diabet Med*. 2008;25:747–50.
29. Vikram NK, Misra A, Pandey RM, Dwivedi M, Luthra K, Dhingra V, et al. Association between subclinical inflammation & fasting insulin in urban young adult north Indian males. *Indian J Med Res*. 2006;124:677–82.



30. Unek IT, Bayraktar F, Solmaz D, Ellidokuz H, Yuksel F, Sisman AR, et al. Enhanced levels of soluble CD40 ligand and C-reactive protein in a total of 312 patients with metabolic syndrome. *Metabolism*. 2010;59:305–13.

UNDER PEER REVIEW