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Original Article

# Significance of Impaired Serum Gelatinases Activities in Metabolic Syndrome

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## ABSTRACT

**Introduction:** A consortium of metabolic risk factors accelerate the onset of diabetes, heart disease, stroke, and certain cancers. Proteolytic enzymes like matrix metalloproteinases (MMP) are regulated by a group of endogenous proteins called tissue inhibitors of metalloproteinases (TIMP). These TIMPs binds to active and alternate sites of activated MMPs and facilitate regulation. Impaired expression of MMPs may have a significant contribution in the pathogenesis of many tissues-destructive processes like tumor progression and cardiovascular and metabolic disorders. **Materials and Methods:** This case control study lays stress on the possible role of impaired levels of circulating MMP-2 and 9 in metabolic syndrome (MetS). The age, sex-matched 388 subjects with 190 newly diagnosed patients, and 198 healthy controls were recruited. To screen the patients with MetS, biochemical analysis of patients for impaired glucose level, hypertension, body mass index (BMI), and lipid profile was performed. The circulating level of MMP-2 and -9 in serum was analyzed by enzyme-linked immunosorbent assay (ELISA) in all patients and control. **Results:** All metabolic risk factors were statistically significant ($P < 0.01$) in patients against control group. The serum MMP-2 and -9 level was significantly higher ($P < 0.001$) in patients having MetS as compared with control group. **Conclusions:** Similar trend was observed in gender wise analysis of serum MMP level. Higher MMP level alteration observed in male patients as compared with female patients.

**Key words:** Insulin resistance, metabolic syndrome, matrix metalloproteinases-2, matrix metalloproteinases-9

## INTRODUCTION

Matrix metalloproteinases (MMPs) act as effectors of extracellular matrix remodeling in physiological and pathological conditions.[1] MMPs can be subdivided according to substrate affinity profile. Of this unlike family of enzymes, MMP-2 and -9 (also known as gelatinase A and gelatinase B, respectively) have come out as important players in a number of pathophysiological conditions in diabetes[2] and cardiovascular disorders.[3] MMP-2 is constitutively expressed on cell surface, whereas MMP-9 is stored in secretory granules, and it is inducible by exogenous stimuli, such as cytokines, growth factors, and cell-matrix contacts.[4,5]

Metabolic syndrome (MetS) is a global problem with devastating human, social, and economic impact and has an alarming prevalence among populations. It predisposes the individuals to a high risk for the development of type 2 diabetes mellitus (T2DM) and coronary artery disease.[6] In India, several studies have shown different rates of prevalence in different parts of the country. Deepa *et al*., 2007,[7] found the prevalence of MetS in south Indian population to be 25.8% by International Diabetes Federation (IDF) as

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Quick Response Code:

Website: www.toxicologyinternational.com

DOI: 10.4103/0971-6580.128818

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compared with 18.3% by Adult Treatment Panel III (ATP III). The Indian Council of Medical Research (ICMR) task force[8] collaborative study reported the prevalence of MetS to be 30% in urban areas of Delhi and 11% in rural Haryana using ATP III criteria. Another study conducted in rural area of district Wardha, Maharashtra who found that the overall prevalence of MetS was 9.3%.[9] The increasing rate of incidence of MetS creates much interest toward research on this. The role of matrix enzymes in MetS is not clear while few reports are available. In MetS subjects, Goncalves *et al*., 2009,[10] reported an increase in pro-MMP-9 and tissue inhibitors of metalloproteinases (TIMP)-1 levels, associated with raised concentrations of inflammatory markers and adhesion molecules but no differences in MMP-2 and TIMP-2 values in comparison with healthy controls. While Hopps *et al*., 2013,[11] reported a significant increase in plasma concentrations of MMP-2, MMP-9, TIMP-1, and TIMP-2 in the whole group of MetS subjects as compared with healthy control. Earlier studies described altered concentrations of gelatinases in various components of MetS as in obesity,[12] dyslipedemia,[13] diabetes,[14,15] and hypertension.[16] MetS rapidly increasing in Indian population due to change in lifestyle. In the present study, we have tried to find out the status of MMP-2 and MMP-9 in MetS in north Indian population. In best of our knowledge no previous report is available on activity of MMPs in MetS in Indian scenario.

## MATERIALS AND METHODS

### Study subjects

A total of 190 MetS patients were recruited according to National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines.[17] Age and ethnicity matched healthy individuals ($n$ = 198) were recruited as controls who were without MetS, non-alcoholic, non-diabetic, and who had no cardiac, respiratory, inflammatory, endocrine, or metabolic disease. All the participants in the study were unrelated individuals of similar ethnicity from Lucknow and other adjoining areas of northern India. Information on demographic features was obtained through personal interview using a standard clinical proforma. All subjects (Cases and controls) gave informed consent for this study, which was reviewed and approved by the ethical review board of this institute.

### Anthropometric measurements

For primary screening of patients with MetS, we followed NCEP-ATP III guidelines for anthropometric measurements.

### Waist circumference

Waist circumference (WC) was measured midway between the margin of the lowest ribs and the iliac crest, at the point of minimal inspiration.

### Blood pressure measurement

The systolic and diastolic blood pressure in subjects were measured for diagnosis of MetS, as it is one of the component of MetS.

### Biochemical estimations

#### *Estimation of fasting plasma glucose*

Blood glucose was determined in the morning in fasting condition from subject's blood samples without preliminary treatment by using Cobas C-111analyzer (Roche) and related kit for estimation.

#### *Estimation of serum lipid profile*

Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG) were estimated by using Cobas C-111analyzer (Roche) and related kit in serum.

### Evaluation of serum MMP level

The serum MMP-2 and MMP-9 level was measured by using a commercially available kit, according to the manufacturer's protocol (Antagene: Human MMP-2 enzyme-linked immunosorbent assay (ELISA) Kit Cat no. EK0459, Human MMP-9 ELISA Kit Cat no. EK0465) with sensitivity of <5 pg/ml.

### Statistical analysis

All the clinical and biochemical data presented as mean ± standard deviation (SD). Statistical analysis was conducted by using SPSS Version 16.0. Comparisons between groups were made by using Student's $t$-test. For all analyses, $P < 0.01$ was considered as statistically significant.

## RESULTS

The patients for the study were primarily screened on the basis of clinical symptoms including WC and blood pressure. Biochemical estimation of risk factors was done for further confirmation of presence of MetS according to NCEP-ATP III criteria. We have included those patients who fulfilled all criteria of MetS.

### Anthropometric measurements in patients and control group

In our study, there was a significant change in anthropometric parameters between patients and control group. The WC (94.17 ± 10.39 vs 82.67 ± 12.13, $P < 0.01$) was significantly different in patients and control group. Weight (76.88 ± 16.49 vs 62.59 ± 8.38, $P < 0.01$) was also significantly altered, whereas there was no significant difference in height (164.86 ± 7.69 vs 165.92 ± 7.72, $P \geq 0.01$) between both groups [Table 1].

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### Blood pressure

Systolic and diastolic blood pressure (136.81 ± 9.90 vs 123.01 ± 7.48 and 87.31 ± 6.88 vs 82.01 ± 3.81, $P < 0.01$) was significantly different in patients against control group [Table 1].

### Glycemic status

The glycemic status was significantly different in both groups. The fasting plasma glucose (112.29 ± 17.44 vs 97.97 ± 9.69, $P < 0.01$) level was significantly altered in patients against control group [Table 1].

### Lipoprotein variables

Lipid profile was altered between both groups. High-density lipoprotein-cholesterol (HDL-C) (41.25 ± 12.05 vs 51.62 ± 8.95, $P < 0.01$) and TG (162.81 ± 77.32 vs 109.73 ± 39.18, $P < 0.01$) were found to be significantly changed in cases as compared with control group [Table 1].

### Enzymatic characterization

Our results showed that the mean level of serum MMP-2 in MetS patients (39.13 ± 19.96 ng/ml) is higher than the mean level of serum MMP-2 in control group (17.59 ± 5.6 ng/ml), and this rises to a significant level with $P < 0.001$ [Table 2]. Similar results we have found in MMP-9 level between patients (73.93 ± 33.59) and control (34.78 ± 12.06) and changes were statistically significant as $P < 0.001$ [Table 2].

Further gender wise observations of serum MMP-2 level (43.09 ± 21.96 vs 20.1 ± 6.71 in male group, whereas 36.63 ± 17.34 vs 15.37 ± 4.17 in female group) and serum MMP-9 level (80.26 ± 37.33 vs 35.35 ± 12.56 in male group, whereas 68.29 ± 27.96 vs 34.35 ± 11.64 in female group) suggest that both were significantly ($P < 0.001$) higher in patients with respect to their control [Table 3]. The results showed higher MMP level in male patients as compared with female patients. In our studied population, larger quantitative changes in MMP-9 level were observed in patients against control as compared with changes in MMP-2 level.

**Table 1: Metabolic risk factor profile in patients and control group**

| Characteristics | Controls ($n$=198) | Cases ($n$=190) | $P$ value |
|---|---|---|---|
| Mean age | 34.43±10.66 | 38.13±15.58 | NS |
| Gender | | | |
| M/F | 91/107 | 89/101 | NS |
| Anthropometric status | | | |
| Height (cm) | 165.92±7.72 | 164.86±7.69 | NS |
| Weight (kg) | 62.59±8.38 | 76.88±16.49 | ≤0.01* |
| WC (cm) | 82.67±12.13 | 94.17±10.39 | <0.01* |
| Fasting plasma glucose (mg/dl) | 97.97±9.69 | 112.29±17.44 | <0.01* |
| Blood pressure (mmHg) | | | |
| Systolic | 123.01±7.48 | 136.81±9.90 | <0.01* |
| Diastolic | 82.01±3.81 | 87.31±6.88 | <0.01* |
| Lipid profile (mg/dl) | | | |
| TC | 147.58±30.38 | 178.52±41.99 | <0.01* |
| TG | 109.73±39.18 | 162.81±77.32 | <0.01* |
| HDL-C | 51.62±8.95 | 41.25±12.05 | <0.01* |
| LDL-C | 95.39±31.70 | 103.23±42.36 | <0.01* |

Data are means±SD; *$P$<0.01 vs control group. WC = Waist circumference, TC = Total cholesterol, TG = Triglycerides, HDL-C = High-density lipoprotein-cholesterol, LDL-C = Low-density lipoprotein-cholesterol, M/F = Male/female, NS = Not significant

**Table 2: Serum MMP level in all studied subjects**

| Serum MMP level (ng/ml) | Study groups ($n$=388) (patients=190, control=198) | $P$ value |
|---|---|---|
| Serum level of MMP-2 | Patients (39.13±19.96) vs control (17.59±5.6) | 0.001* |
| Serum level of MMP-9 | Patients (73.93±33.59) vs control (34.78±12.06) | 0.001* |

Data are means±SD; *$P$<0.001 vs control group. MMP-2 = Matrix metalloproteinase-2, MMP-9 = Matrix metalloproteinase-9

**Table 3: Gender wise serum MMP-2 and -9 level in patients and control groups**

| Gender | MMP | Serum MMP level (ng/ml) | $P$ value |
|---|---|---|---|
| Male Patients=89, Control=91 | MMP-2 | Patients (43.09±21.96) vs control (20.1±6.71) | 0.001* |
| | MMP-9 | Patients (80.26±37.33) vs control (35.35±12.56) | 0.001* |
| Female Patients=101, Control=107 | MMP-2 | Patients (36.63±17.34) vs control (15.37±4.17) | 0.001* |
| | MMP-9 | Patients (68.29±27.96) vs control (34.35±11.64) | 0.001* |

Data are means±SD; *$P$<0.001 vs control group. MMP-2 = Matrix metalloproteinase-2, MMP-9 = Matrix metalloproteinase-9

## DISCUSSION

The research attention in MMPs has drastically increased during the past few years, as they pose to be a pertinent target for cardiovascular and related diseases. Different components of MetS have been recognized as a probable stimulus for the synthesis and activity of metalloproteinases.[18] Several *in vitro* and *in vivo* studies suggested that glucose plays an important role in MMPs regulation. The metabolic abnormalities of diabetes cause mitochondrial superoxide overproduction. This increased superoxide production is the fundamental and major pathway resulting in deregulation of endothelial nitric oxide synthase (eNOS) activity, an increased expression and activity of MMP-2 and MMP-9 mediator of diabetes tissue damage.[19] When hyperglycemia impairs activation of the insulin signal and reduced TIMP-3 were observed in coronary endothelial cells[20] and in atherosclerotic

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plaques from subjects with type 2 diabetes.[21] Death *et al.*, 2003,[22] showed that MMP-1, MMP-2, and MMP-9 are more expressed by diabetic cultured endothelial cells and monocyte-derived macrophages under the influence of an elevated glucose concentration. Additionally, they noted a decrease in MMP-3, but no significant effects on TIMP-1 expression were found.

While examining the data for MMPs pattern in obesity-ridden subjects, altogether contrasting observations came to be noted. In a comparison between obese and lean women, higher concentrations of plasma MMP-9 and TIMP-1 and lower concentrations of MMP-2 were noted in the former as compared with the latter.[23] Some groups also reported opposite findings of increased MMP-2 and MMP-9 levels in obese subjects[12] suggesting toward an abnormal extracellular matrix metabolism. In obese hypertensive MMP-9 correlated with body mass index (BMI), systolic blood pressure, and fasting plasma insulin and found to be higher than normal individuals.[24] The messenger RNA (mRNA) expression of MMP-9 by adipocytes and macrophages in the adipose tissue was reported to be elevated in obese and insulin-resistant subjects that lower down after pioglitazone treatment.[25]

It was reported that oxidized form of LDL upregulates MMP-9 expression and reduce TIMP-1 expression in cultured monocyte-derived macrophages, promoting the atherosclerotic process in hyperlipidemic subjects.[26] This construes that MMP-9 plasma levels could be considered an an early indicator of atherosclerosis.[27] Another study showed that lipoprotein lowering drug pravastatin decreases MMP-9 concentration in mild hypercholesterolemic men independently of changes in lipid levels, indicative of a pleiotropic effect.[28] Higher levels of MMP-2, MMP-9, TIMP-1, and TIMP-2 have been reported in untreated subjects with mild combined dyslipidemia.[13] Plasma MMP-9, TIMP-1, and TIMP-2 were found to be higher in MetS subjects associated to familial combined hyperlipidemia than in those with MetS alone, and their plasma level could be diagnostic marker of MetS.[29] The sequence variation in promoter region of MMP-2 gene was reported to be associated with genetic risk of MetS.[30]

Our results showed similar outcomes as earlier reported by Hopps *et al.*, 2013,[11] their study reported significant increased plasma level of gelatinases and respective inhibitors in patients with MetS. They also reported significant increased activity of MMP-2, MMP-9, and their inhibitors in diabetic patients with MetS. Our study was also supported by other similar reports in different populations;[29] higher plasma MMP-2 activity was reported in women with MetS,[31] whereas partially supported with other reports in different parameters related to MetS.[15] Our study does not match with the study conducted by Gummensson *et al.*, 2009,[32] as their group reported circulating level of MMP-9 in patients with MetS presented slightly higher when using the IDF classification of MetS but not with the World Health Organization (WHO) or NCEP classification. However, others reported contradictory results, with no differences in MMP-2 activity and higher levels in MMP-9 activity in MetS patients in comparison with controls or increased level of other MMPs, like MMP-8.[10] No differences in MMP-9 comparing pre- and postmenopausal women with and without MetS observed among groups, even after the use of estrogen therapy.[33] There is no absolute justification regarding these conflicting reports.

It is well established that MetS is coupled to a proinflammatory state. The evidence lies in the presence of elevated concentrations of various inflammatory molecules and cytokines, along with a concomitant decrease in anti-inflammatory molecules.[18] MMPs are subjected to coexpression or corepression in response to inflammatory cytokines and growth factors. In the absence of new protein synthesis and sufficient cellular stimulation, the MMP promoters are induced. These promoters are downstream targets within signaling pathways of early response genes. The intermediate activators of the above mentioned signaling pathways are a large variety of ligands like interleukin-1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α), nuclear factor kappa B (NF-κB), and mitogen-activated protein kinase (MAPK).[34]

In conclusion, we found that serum MMP-2 and MMP-9 level in patients suffering with MetS were significantly increased in our studied population. However, to establish the mechanism behind the increased gelatinases activity needs an extensive study on a bigger sample size.

## ACKNOWLEDGMENT

This study was funded by the ICMR, New Delhi, India with Grant No 52/15/2008-BMS sanctioned to Dr S. Khattri. The author S.S. Yadav is thankful to ICMR for providing senior research fellowship during the course of study.

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**How to cite this article:** Yadav SS, Singh MK, Dwivedi P, Mandal RK, Usman K, Khattri S, *et al.* Significance of impaired serum gelatinases activities in metabolic syndrome. Toxicol Int 2014;21:107-11.

**Source of Support:** ICMR, New Delhi, India with Grant No 52/15/2008-BMS.
**Conflict of Interest:** None declared.