Evaluation of Serum Prolidase Activity and Oxidant–Antioxidant Status in Metabolic Syndrome - A Cross-Sectional Study in VIMSAR, Burla

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ABSTRACT

BACKGROUND

Prolidase, a member of the matrix metalloproteinase (MMP) family, is a cytosolic imido dipeptidase, which specifically splits imido dipeptides with C-terminal proline or hydroxyproline. We wanted to compare the serum levels of prolidase enzyme activity & total antioxidant status in patients with metabolic syndrome. Increased prolidase activity and decreased total antioxidant status may indicate critical biological activities relevant to pathological events in metabolic syndrome (MetS), and this activity may be a biological indicator of disease.

METHODS

This cross-sectional study was conducted in the Department of Biochemistry, Veer Surendra Sai Institute of Medical Sciences and Research, Burla. Out of a total of 135 subjects, 45 had metabolic syndrome, 45 were obese without metabolic syndrome and 45 were non-obese healthy controls.

RESULTS

In MetS group, prolidase levels were significantly higher when compared to obese and control groups ($P < 0.001$ and $P < 0.05$ respectively) and also in obese group against control group ($P < 0.05$). Tacrolimus (TAC) levels were also lesser in MetS and obese groups when compared to those of control group ($P < 0.001$ and $P < 0.05$ respectively). Prolidase was negatively correlated with TAC and high density lipoprotein (HDL-C); $r = -0.33$, $P < 0.1$; $r = -0.35$, $p < 0.08$ and positively correlated with body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL-C) & TOS ($r = 0.42$, $P = 0.03$; $r = 0.39$ $P = 0.05$; $r = 0.40$ $P < 0.04$; $r = +0.44$, $P = 0.02$; $r = 0.39$, $P = 0.05$; $r = 0.41$, $P = 0.04$ and $r = 0.4$, $P = 0.04$, respectively.

CONCLUSIONS

Increased prolidase activity is closely associated with the medical phenotype of the metabolic syndrome. Increased prolidase activity and decreased total antioxidant status may indicate critical biological activities relevant to pathological events in Mets, and this activity may be a biological indicator of disease.

KEYWORDS

Serum Prolidase, Oxidant Antioxidating Status and Metabolic Syndrome

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DOI: 10.18410/jebmh/2021/247

How to Cite This Article:
Acharya M, Bhoi S, Yadav MK. Evaluation of serum prolidase activity and oxidant–antioxidant status in metabolic syndrome - a cross-sectional study in VIMSAR, Burla. J Evid Based Med Healthc 2021;8(18):1293-1298. DOI: 10.18410/jebmh/2021/247

Submission 17-01-2021,
Peer Review 24-01-2021,
Acceptance 19-03-2021,
Published 03-05-2021.

BACKGROUND

As per definition, existence of obesity, resistance to insulin, intolerance to glucose, dyslipidaemia and hypertension is regarded as metabolic syndrome (MetS).[1] All obese subjects might not be MetS but all MetS subjects are obese. Impacts on cardiovascular mortality and morbidity have been shown in both MetS and obesity.[2] Hence one of the leading global public health concerns include Metabolic syndrome .[3] The worldwide prevalence of the syndrome in adult population is predicted to be 20 % - 25 %.[4] In India it is 11 % - 56 %.[5] World health organization (WHO) globally estimated around 16 % adults to be overweighed and 5 % to be obese.[6] In India 6 % of women and 9.3 % of men are obese.[7] Micro and macrovascular complications are caused by alterations in the arterial vasculature leading to endothelial malfunction. The erosion and thrombosis due to remodelling of the endothelial basal membrane increases oxidative stress and alters expression of matrix metalloproteinases (MMPs).[8] Cytosolic imido dipeptidase, a member of MMP family named Prolidase, exclusively splits C-terminal proline or hydroxyproline of imido dipeptides. The enzyme there after accentuates in salvage of proline for re-synthesis of collagen and other proline proteins.[9] Plasma, erythrocytes, leukocytes, dermal fibroblasts and various organs such as kidney, brain, heart, thymus, uterus, lung, spleen and pancreas have been shown to have prolidase enzyme activity.[10,11] In different disorders like chronic liver disease, osteoporosis, osteoarthritis, uraemia, and hypertension this enzyme have been implicated to have a role.[12,13] To our best knowledge, there is hardly any data regarding serum prolidase activity and oxidant–antioxidant status in metabolic syndrome. Increased prolidase activity is closely associated with the medical phenotype of the metabolic syndrome. Increased prolidase activity and decrease total antioxidant status may indicate critical biological activities relevant to pathological events in Mets, and this activity may be a biological indicator of disease.

We intend to compare the serum levels of prolidase enzyme activity & total antioxidant status in patients with metabolic syndrome.

METHODS

This cross-sectional study was conducted in the Department of Biochemistry, Veer Surendra Sai Institute of Medical Science and Research, Burlain in collaboration with Department of General Medicine from November 2019 to November 2020.

Study Population

Cases: In-patients and out-patients of post graduate (PG) department of Medicine. VIMSAR, selected as per: ATP III 2001 guidelines, any three of the following; a) Waist circumference: male - > 102 cm and female > 88 cm. b) Higher TG: $\geq$ 150 mg / dl. c) Low HDL–cholesterol: < 40 mg / dl in males and < 50 mg / dl females. d) Raised blood pressure: systolic BP $\geq$ 130 mm Hg or diastolic BP $\geq$ 85 mm Hg or on treatment and f) raised fasting blood sugar: $\geq$ 100 mg / dl. Control: age, sex, socioeconomic status matched normal, non-obese individuals. Out of 135, 45 metabolic syndrome, 45 obese without metabolic syndrome and 45 non-obese healthy controls.

Sample Size Calculation

$$SS = Z^2 \times (p) \times (1 - P) / c2$$

$$SS = 3.84 \times 0.9 / 0.0025 = 136$$

Where,
SS = sample size.
Z = Z-value A (e.g.; 1.96 for a 5 % level of significance).
P = Prevalence (10 %) percentage of population, expressed as decimal.
C = Precision or margin of error, expressed as decimal (0.05).
Note: 136 divided into each group in 45.

Inclusion Criteria

- Obese subjects having BMI ≥ 30 kg / m^2 according to WHO criteria, between the age group 25 - 50 years without metabolic syndrome.
- Patients between age group 25 - 50 years with metabolic syndrome screened as per the Adult Treatment Panel III 2001 (ATPIII) criteria of the National Cholesterol Education Program (NCEP).
- Willing to participate in the study.

Exclusion Criteria

- Participants having heart failure, cirrhosis, osteoarthritis, kidney failure, pregnancy or malignancy.
- Patients who were critically ill.

Anthropometric and Biochemical Analysis

Various anthropometric parameters like age, body weight, height, BMI and BP were recorded in all participants. Fasting blood sugar (HDL-C, LDL-C, Total cholesterol, Triglyceride, were analyzed on fully automated (COBAS C 311) analyser machine for all subjects. The work was approved by the Institutional ethical committee, prior to written informed consent from all participants.

Serum Prolidase Activity Measurement

Serum prolidase activity was calculated by enzyme linked immunoassay (ELISA) technique (Erba) as per manufacturer's instructions.

Measurement of Total Antioxidant Capacity (TAC)

Erel's automated method was used to determine total oxidant activity (TOA).[14] Here, the sample's antioxidative effect was measured against potent-free radical reactions

(initiated by a hydroxyl radical) and the results expressed as µmol Trolox eq. / L.

Measurement of Total Oxidant Activity (TOA)

Erel's automated method was used to determine total oxidant activity (TOA).[15] Calibration of the assay was done using hydrogen peroxide and expressed as µmol H2O2 equiv. / L.

Oxidative Stress Index (OSI)

The degree of oxidative stress, expressed as OSI was calculated as: OSI (arbitrary units) = [TOA / TAC] × 100.[14]

Statistical Analysis

Mean ± SD was used to express results, and analyzed by using One-way analysis of variance (ANOVA) with "P" value < 0.05 for significance and Pearson correlation coefficient was used to evaluate any relationship between different variables.

RESULTS

The study was done between the age group of 25 to 56 years with mean age of the MetS group was 43.56 ± 4.54 years and of the obese was 38.26 ± 7.19 years and of the control was 41.10 ± 6.39 years. The male female ratio was 16:9, 15:10, 17:8 for the MetS, obese and control group respectively. In the MetS group, SBP, DBP, TC and TG levels were significantly higher as compared to obese and control groups (all P < 0.001) (Table 1). Significantly higher BMI levels in obese and MetS groups was observed against controls (P < 0.0001). SBP and DBP was seen to be higher in obese group than control group (P < 0.001). The mean fasting blood sugar (FBS) in the MetS, 120. 48 ± 28. 84 mg / dl was higher as compared to the obese 90.90 ± 7.87 mg/dl and controls 89.12 ± 9.99 mg / dl respectively, the difference in FBS was statistically highly significant. The mean FBS in the obese was 90.90 ± 7.87 mg / dl and in controls was 89.12 ± 9.99 mg / dl, the difference was statistically not significant (P < 0.001). In our study on evaluating the lipid profile, serum total cholesterol was found to be higher in MetS (201.84 ± 20.88 mg / dl) when compared to the obese (158.94 ± 19.96 mg / dl) and the controls (157.88 ± 26.14 mg / dl), which was statistically highly significant respectively. The mean TC in the obese was 158. 94 ± 19.96 mg / dl and in control was 157. 88 ± 26.14 mg / dl, the difference was statistically not significant. Elevated triglyceride level and low HDL-C level are components of metabolic syndrome. In our study higher triglyceride was observed in MetS group 183.38 ± 36.00 mg / dl compared to obese 110.14 ± 22.47 mg / dl and control group 109.50 ± 23.08 mg / dl, which was statistically significant respectively. The mean TG in the obese was 110.14 ± 22.47 mg / dl and in controls was 109.50 ± 23.08 mg / dl, the difference was statistically not significant. Significantly lower HDL-C was seen in MetS group than controls (P < 0.001). However, HDL-C levels were insignificantly lower in the obese group compared to control group.

In MetS group, prolidase levels were significantly higher when compared to obese and control groups and also in obese group against control group (P < 0.001). TAC levels were also lesser in MetS and obese groups when seen against control group (P < 0.001). However, insignificant difference in BMI levels was observed between MetS and obese groups as shown in Table 1.

Variables	Control (N = 45) [Mean ± SD]	Obese (N = 45) [Mean ± SD]	Mets (N = 45) [Mean ± SD]	ANOVA (P Value)
Age in years	41.10 ± 6.39	38.26 ± 7.19	43.56 ± 4.54	NS**
BMI in (Kg / m^2)	22.22 ± 1.62	32.74 ± 1.02	26.96 ± 3.01	0.001*
Waist circumference in (cm)	86.24 ± 6.57	116.06 ± 7.26	103.00 ± 8.25	0.001*
SBP (mm Hg)	119.52 ± 9.44	124.40 ± 5.63	132.92 ± 14.02	0.001*
DBP (mm Hg)	79.84 ± 6.26	80.04 ± 2.16	89.04 ± 10.69	0.001*
FBS (mg / dl)	89.12 ± 9.99	90.90 ± 7.87	120.48 ± 28.84	0.001*
Total cholesterol (mg / dl)	157.88 ± 26.14	158.94 ± 19.96	201.84 ± 20.88	0.001*
Triglycerides (mg / dl)	109.50 ± 23.08	110.14 ± 22.47	183.38 ± 36.00	0.001*
HDL-C (mg / dl)	41.40 ± 8.88	40.90 ± 6.72	37.70 ± 6.26	0.01*
LDL-C (mg / dl)	91.36 ± 25.73	92.24 ± 15.04	125.16 ± 19.07	0.001*
TOA (mmol H2O2 Equiv./ l)	11.2 ± 2.5	10.8 ± 2.4	11.6 ± 2.6	NS**
TAC (mmol Trolox Equiv. / l)	1.14 ± 0.2	1.12 ± 0.2	0.93 ± 0.1	0.001*
OSI (H2O2 / Trolox)	9.21 ± 23	10.72 ± 2.5	13.9 ± 3.2	NS**
Serum prolidase (ng / ml)	28.86 ± 3.39	35.40 ± 4.03	41.49 ± 6.59	0.001*

Table 1. Demographics and Clinical Parameters of Different Groups

(ANOVA-* Statistically Significant at P value < 0.05; **Statistically not significant P > 0.05)

Parameters	Prolidase (r)	P-Value
BMI in (Kg / m^2)	+ 0.42	0.03
Waist circumference in (cm)	+ 0.39	0.05
SBP (mmHg)	+ 0.40	0.04
DBP (mmHg)	+ 0.44	0.02
Total cholesterol (mg / dl)	+ 0.41	0.04
Triglycerides (mg / dl)	+ 0.39	0.05
HDL-C (mg / dl)	- 0.35	0.08
LDL-C (mg / dl)	+ 0.4	0.04
TAS (mmol Trolox Equiv. / l)	- 0.33	0.1

Table 2. Correlation between Prolidase & Different Parameters of Mets

	Control		Obese without Mets		Case (Mets)	
A	B	C	D	E	F	G
F (8,36)	4.993		1.681		23.231	
P-value	.000^c		.137^c		.000^c	
R^2	.526		.272		.838	
(Constant)	34.976	P-value	- 12.513	P Value	- 41.008	P-value
BMI	-.728	.019	.306	.616	.395	.076
WC	.029	.693	-.061	.582	.505	.000
SBP	.223	.002	.257	.096	.042	.449
DBP	-.300	.014	.131	.664	.112	.081
TC	-.037	.609	.269	.005	-.001	.998
TG	.007	.787	-.055	.097	-.012	.770
HDL	.078	.315	-.253	.037	.006	.981
LDL	.073	.290	-.254	.024	.052	.818

Table 3. Group Wise (Control, Obese without Metabolic Syndrome, & Cases with Metabolic Syndrome) Multiple Linear Regression Analysis

Table 2. shows negative correlation between prolidase with TAC and HDL – C; (r = – 0.33, P < 0.1) (r = – 0.35, P < 0.08) and positively correlated with BMI, waist-c, SBP, DBP, TG, TC, LDL-C & TOS (r = 0.42, P = 0.03) (r = 0.39, P

= 0.05); (r = 0.40, P < 0.04); (r = + 0.44, P = 0.02); (r = 0.39, P = 0.05); (r = 0.41, P = 0.04) and (r = 0.4, P = 0.04), respectively.

A multiple linear regression analysis (Groupwise i.e., according to control, obese without metabolic syndrome, & cases with metabolic syndrome) was done to predict the value of prolidase from BMI, waist circumference (WC), systolic blood pressure, diastolic blood pressure, total cholesterol, total triglycerides, HDL, LDL.

A. In control group all the above-mentioned variables statistically significantly predicted (combined) the value of Sr. prolidase (F (8, 36) = 4.993, P < 0.005, R^2 = 0.526). But BMI, SBP, DBP added statistically significantly to the predication as P < 0.05 (Column-C). Value of prolidase in control group (Column-B) = 34.976 - (0.728) (BMI) + (0.029) (WC) + (0.223) (SBP) - (0.3) (DBP) - (0.037) (TC) + (0.007) (TG) + (0.078) (HDL) + (0.073) (LDL)
B. n group with obese without metabolic syndrome all the above-mentioned variables not significantly predicted (combined) the value of Sr. Prolidase (F (8,36) = 1.681, P > 0.05, R^2 = 0.272). But SBP, TC, HDL, LDL added statistically significantly to the predication as P < 0.05 (Column-E). Value of prolidase in obese without met group (Column-D) = - 12.513 + (0.306) (BMI) - (0.061) (WC) + (0.257) (SBP) + (0.131) (DBP) + (0.269) (TC) - (0.055) (TG) - (0.253) (HDL) - (0.254) (LDL)
C. In group with metabolic syndrome all the above-mentioned variables statistically significantly predicted (combined) the value of Sr. Prolidase (F (8, 36) = 23.231, P < 0.005, R^2 = 0.838). But only WC added statistically significantly to the predication as P < 0.05 (Column-G). value of prolidase in control group (Column-F) = - 41.008 + (0.395) (BMI) + (0.505) (WC) + (0.042) (SBP) + (0.112) (DBP) - (0.001) (TC) - (0.012) (TG) + (0.006) (HDL) + (0.052) (LDL)

DISCUSSION

In the present study, the metabolic syndrome was defined using modified NCEP-ATP III criteria approved for the Asian population. This study was carried out to calculate the difference between the level of serum prolidase in the patients with metabolic syndrome, obese patients without metabolic syndrome and healthy controls. The prevalence of metabolic syndrome in Asian Indians fluctuate according to the geography, levels of urbanization, pattern of lifestyle and socioeconomic / cultural factors. Asian Indians are high-risk population with respect to MetS and the numbers are consistently on the rise. Statistics in India is almost equivalent to the world population regarding the prevalence of MetS and surprisingly the prevalence in India is more in women than in men, both in rural as in urban population.

The BMI in MetS, 26.96 ± 3.01 kg / m^2 was higher compared to the controls 22.22 ± 1.62 kg / m^2, the difference was significantly high. This finding was supported by the study done by Rubin et al.[16] who observed significantly higher BMI in the MetS compared to healthy controls. The BMI in obese 32.74 ± 1.02 kg / m^2 was higher than MetS 26.96 ± 3.01 kg / m^2 and controls 22.22 ± 1.62 kg / m^2 respectively, the difference was statistically highly significant.

The mean waist circumference in MetS 103.00 ± 8.25 cm was higher compared to the controls 86. 24 ± 6.57 cm, the difference was highly significant. This finding was supported by the study done by Rubin et al.[16] who observed significantly higher waist circumference in the MetS patients compared to the healthy controls. The mean waist circumference in obese 116.06 ± 7.26 cm was higher than MetS 103.00 ± 8.25 cm and controls 86.24 ± 6.57 cm respectively, the difference was statistically highly significant.

MetS group had higher SBP 132.92 ± 14.02 mmHg than obese 124. 40 ± 5.63 mm Hg and control group 119.52 ± 9.44 mm Hg respectively. The difference was statistically highly significant. Obese group had higher SBP 124.40 ± 5.63 mm Hg than control group 119.52 ± 9.44 mm Hg. The difference was statistically significant. MetS group had higher DBP 89.04 ± 10.69 mm Hg than obese 80.04 ± 2.16 mmHg and control group 79.84 ± 6.26 mm Hg respectively. The difference was statistically highly significant. The mean DBP in the obese was 80.04 ± 2.16 mmHg and in controls was 79.84 ± 6.26 mm Hg, the difference was statistically not significant. The systolic and diastolic blood pressure in MetS was higher as compared to control group. The present study was supported by a similar study by Chuang et al.[17] who observed prevalence of high blood pressure among patients with metabolic syndrome.

High density lipoprotein was found to be lower in the MetS 37.70 ± 6.26 mg / dl when compared to the controls 41.40 ± 8.88 mg / dl, which was statistically significant. These findings were similar to the results of the study done by Miwa Ryo et al.[18] High density lipoprotein (HDL) was also found to be lower in the MetS 37.70 ± 6.26 mg / dl when compared to the obese 40.90 ± 6.72 mg / dl, which was statistically significant. The mean HDL in the obese was 40.90 ± 6.72 mg / dl and in controls was 41.40 ± 8.88 mg / dl, the difference was statistically not significant. Marroquin et al. found in his study that the mortality associated with metabolic syndrome cases is due to to the cardiovascular diseases which is aggravated by atherogenic dyslipidaemia such as elevated triglyceride and low HDL-C. High density lipoprotein is involved in reverse cholesterol transport which is protective for cardiovascular diseases. So, low levels of HDL-C in MetS is a risk factor for CVD.[19]

The mean LDL-C in the MetS 125.16 ± 19.07 mg / dl was higher compared to the obese 92.24 ± 15.04 mg / dl and controls 91.36 ±2 5.73 mg / dl, the difference was statistically highly significant. The mean LDL-C in the obese was 92.24 ± 15.04 mg / dl and in controls was 91.36 ± 25.73 mg / dl, the difference was statistically not significant. Dyslipidemia along with hypertension were well-established and moderately overlapping threat for cardiovascular disease. Moreover, hypertension and dyslipidaemia was understood to be manifestations in metabolic syndrome, which is a consequence of the gene interaction with the environment. The pathogenesis in hypertension and dyslipidaemia is somewhat understood but endothelial dysfunction plays an underlying role in both.

The matrix metalloproteinases, prolidase, plays a vital role in metabolism of collagen and remodelling of extracellular matrix. Increased prolidase activity indicates increased collagen turn over which occurs during the conditions of metabolic stress. In MetS, serum prolidase 41.49 ± 6.59 ng / ml was observed to be superior against controls 28.86 ± 3.39 ng / ml, the difference was statistically highly significant. The serum prolidase in the MetS 41.49 ± 6.59 ng / ml was higher compared to the obese 35.40 ± 4.03 ng / ml, the difference was statistically highly significant. The serum prolidase was significantly higher in MetS group compared to the only obese group.

This may be due to presence of hypertension, hypertriglyceridemia, low HDL-C levels, impaired fasting glucose, which are found more frequently in the MetS compared to obesity. The serum prolidase in the obese 35.40 ± 4.03 ng / ml was higher compared to the controls 28.86 ± 3.39 ng / ml, the difference was statistically highly significant.

Reports of few studies enlighten MMPs role in MetS. Goncalves et al. published increased pro-MMP-9, MMP-8 and TIMP-1 levels but no difference in MMP-2, MMP-3 and TIMP-2 levels when match up to healthy controls.[20] Furthermore, increased MMP-8 levels in MetS subjects[21] along with higher MMP-2 activity, but not of MMP-9 was observed in non-diabetic MetS.[22] On another side, few studies were seen regarding MMPs profile in obesity,[23] diabetes mellitus[24] hypertension[25] and dyslipidemia,[26] clinical conditions representing diagnostic criteria for the definition of the metabolic syndrome. We have previously mentioned the alteration of oxidative stress in MetS and obesity affecting atherosclerotic cardiovascular events. In our findings we also mentioned noteworthy increase of OSİ levels and a major decrease of TAC levels in metabolic syndrome compared to obese and healthy control groups concordant to our earlier study.[27]

The results of our study show that the serum prolidase has a strong association with the parameters of the metabolic syndrome. Therefore, it may be possible that increased serum prolidase concentration in metabolic syndrome and decrease in TAC could be considered as an autonomous predictor of the disease.

CONCLUSIONS

Increased prolidase activity is closely associated with the medical phenotype of the metabolic syndrome. Increased prolidase activity and decreased total antioxidant status may indicate critical biological activities relevant to pathological events in Mets, and this activity may be a biological indicator of disease.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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