

Original Research Article

Fetuin-A in association with metabolic syndrome and its components

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ABSTRACT

Background: Fetuin-A also known as α -2-Heremans-Schmid glycoprotein, is a multifunctional plasma glycoprotein. In developing countries like India, the metabolic syndrome (MetS) is on an exponential rise. The factors that characterize MetS are also associated with the atherosclerotic process, in which an important role is played by serum fetuin-A levels. The aim of present study is an assessment of serum fetuin-A level and its association with other components of MetS in age matched healthy controls and MetS subjects.

Methods: Total eighty (N=80) subjects (40 MetS cases and 40 age and gender matched controls) were included based on inclusion and exclusion criteria. The fasting venous samples were collected to measure the fasting glucose, lipid profile, glycated hemoglobin, insulin and fetuin-A levels. The serum fetuin levels were estimated by ELISA kit.

Results: The serum fetuin-A levels were significantly higher in MetS cases as compared to the control group (p value<0.001). Other components like insulin, HbA1c and HOMA-IR levels were raised in MetS compared to controls. In correlation analysis the serum fetuin-A levels were positively correlated with fasting insulin levels (r=0.36, p=0.02), fasting glucose (r=0.39, p=0.01) and triglycerides (r=0.34, p=0.03). Also, in receiver operating characteristic curve analysis the AUC for fetuin-A is 0.76 (95% CI: 0.65-0.86) was observed.

Conclusions: We found that serum fetuin-A levels were strongly and independently associated with MetS. Our finding suggests that fetuin-A could be a useful marker in clinical practice in the future for the early diagnosis of MetS.

Keywords: Fetuin-A, Metabolic syndrome, Insulin

INTRODUCTION

Metabolic syndrome (MetS) is a major public health problem of the present era. It consists of constellation of metabolic abnormalities and physical conditions. Metabolic syndrome is associated with central obesity, hyperinsulinemia, reduced high-density lipoproteins (HDL), higher triglycerides, and hypertension. MetS mainly accompanying with the risk of emerging diabetes and cardiovascular disease. The precise mechanisms of the multifaceted pathogenesis of metabolic syndrome are under exploration. Insulin resistance is thought to be the primary underlying abnormality leading to MetS.¹⁻³ Recently, epidemiologic investigations have suggested that serum fetuin-A was connected with insulin resistance

and its co-morbidities such as type 2 diabetes mellitus and MetS.

Fetuin-A, also known as α -2-Heremans-Schmid glycoprotein (AHSG), it comes under cystatin superfamily protease inhibitors. The fetuin-A expression in among different tissues is controversial. In spite of that fetuin-A is primarily secreted by the liver, recently it has been described that it is expressing in adipocytes and secreting in adipose tissue.^{4,5} In the same way, different group reported that storage of fetuin-A has been observed in bone osteocytes after absorbing from circulation.⁶

Earlier investigations have revealed that fetuin-A majorly involved in physiological and cellular metabolisms like

fatty acid and protein metabolisms, bone metabolism, calcium homeostasis and regulation of inflammation.⁷

However, recently the fetuin-A anticipated as a molecular connection between obesity, insulin resistance, MetS and non-alcoholic fatty liver disease, since fetuin-A shown the inhibitory effect on insulin receptor and which leads to insulin signalling disintegration.⁸ Abundant studies have been noticed that significance of increased fetuin-A levels vascular calcification, bone mineral metabolism, cardiovascular disorders, obesity, insulin resistance and diabetes mellitus. In India, few studies focused on vascular calcification in end stage renal disease and chronic kidney disease.^{9,10}

Recently, in a systematic review and meta-analysis study has exposed the fetuin-A importance in MetS.¹¹ There are no studies to find out the relationship between MetS and fetuin-A particularly in Indian patients so far. The aim of the study was to evaluate the fetuin-A levels in MetS and its components.

METHODS

The present study was a case control study, conducted from January 2016 to June 2017 in department of Biochemistry, Maulana Azad Medical college. It was approved by Institutional Ethics Committee for human studies. The written informed consent was obtained from all participants before conducting the study. Eighty subjects (40 cases and 40 age and gender matched healthy subjects) who is achieving the inclusion and exclusion criteria were enrolled in the study. MetS was diagnosed on the basis of clinical examination with anthropometric measurements were recorded on predesigned proforma. Healthy controls were recruited from the relatives and attendant of the patients and staff working in the hospital. Exclusion criteria was subjects with parathyroid disease, chronic kidney disease, metabolic bone disease and subjects taking drugs like statins and fibrates which can alter serum lipid profile and its estimation.

Blood sample collection and estimation of biochemical parameters

After overnight fasting, 5 ml of blood sample was collected from the subjects. The whole blood sample was used for the analysis of HbA1c and separated serum sample was used for the estimation of fasting glucose, lipid profile. The remaining serum was stored for further parameters analysis namely insulin (Roche diagnostics, Roche, Germany) by electrochemiluminescence (ECL) immunoassay and fetuin-A (Elabscience, USA) by ELISA.

Statistical analysis

The baseline and biochemical parameters data were expressed as mean±standard deviation and median with range. The normality of the data was tested by Kolmogorov-Smirnov test. Independent t-test or Mann-Whitney U test was used to compare the differences between cases and control groups. Statistical analysis was performed using SPSS software and p value<0.05 considered as statistical significance.

RESULTS

Table 1 shows the baseline characteristics of the MetS cases and controls. There was no significant difference in age and height whereas BMI, waist circumference, waist-hip ratio, SBP and DBP were significantly higher in MetS cases. The biochemical parameters of the MetS cases and healthy controls showed (Table 2) significant difference in glucose, lipid profile and HbA1c which are all raised up in MetS. Furthermore, the insulin, HOMA-IR and fetuin-A were significantly elevated in MetS cases. The correlation of fetuin-A with other biochemical parameters in MetS cases were shown in Table 3. Insulin ($r=0.36$, $p=0.02$), glucose ($r=0.39$, $p=0.01$) and triglycerides ($r=0.34$, $p=0.03$) were positively correlated with fetuin-A. There was no significant correlation between HDL with fetuin-A.

Table 1: Mean±SD of baseline characteristics in the controls and MetS cases.

Parameters	Controls (N=40)	MetS cases (N=40)	P value
Age (years)	37.2±9.6	37.7±10.6	0.59
Height (m)	1.62±0.08	1.58±0.07	0.148
Weight (kg)	64.7±8.5	82.8±11.0	0.04
BMI (kg/m ²)	23.4±1.7	32.8±3.6	0.001
Waist circumference (cm)	77.2±6.2	101.4±9.8	0.001
SBP (mmHg)	115.6±7.0	122.9±11.6	0.004
DBP (mmHg)	73.4±6.2	78.2±7.5	0.006

Note: Data were expressed in mean±SD, independent t-test was used for statistical significance, p value<0.05 considered as significant.

Table 2: Mean±SD of biochemical parameters the controls and MetS cases.

Parameters	Controls (N=40)	MetS cases (N=40)	P value
Fasting glucose (mg/dl)	90.3±4.9	113.5±23.2	0.002
Serum TC (mg/dl)	165±35.2	234.5±59.9	0.001
Serum TG (mg/dl)	114.9±17.8	212.0±80.3	0.001

Continued.

Parameters	Controls (N=40)	MetS cases (N=40)	P value
Serum HDL (mg/dl)	52.7±7.8	41.5±7.3	0.001
HbA1c (%)	5.1±0.3	5.8±0.8	0.001
Fasting insulin (µIU/ml)	11.0±3.4	27.7±11.1	0.003
HOMA-IR	1.43±0.44	5.42±3.98	0.001
Serum fetuin-A (µg/ml)	153.3±47.8	219.8±83.1	0.001

Note: Data were expressed in mean±SD, independent t-test was used for statistical significance, p value<0.05 considered as significant.

Table 3: Spearman correlation analysis of fetuin-A with MetS components and other biochemical parameters in MetS cases.

Parameters	R value	P value
Age (years)	-0.07	0.62
BMI	0.29	0.06
Glucose	0.39	0.01*
Insulin	0.36	0.02*
HDL	0.12	0.45
Triglycerides	0.34	0.03*
Total cholesterol	0.19	0.22

Note: *p value<0.05 considered as significant.

Figure 1 shows the Receiver operating characteristic (ROC) curve analysis for fetuin-A cut-off value to predict MetS. At the cut-off value 173.8 (68% sensitivity, 69% specificity, AUC 0.76, and 95% CI: 0.65-0.86), fetuin-A can differentiate the MetS cases with healthy controls.

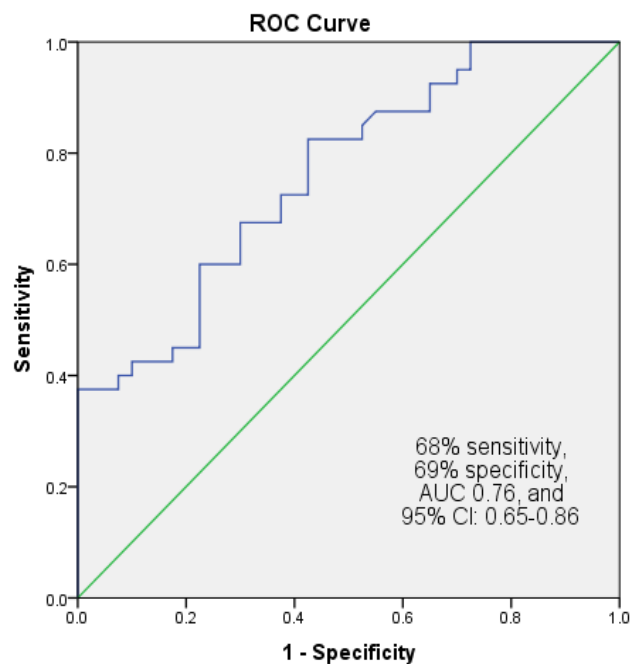


Figure 1: Receiver operating characteristic curve analysis to show the fetuin-A at 173.8 (µg/ml) as a predictor of MetS cases.

DISCUSSION

MetS is a contemporary global phenomenon linked to a highest risk of having other chronic diseases including diabetes mellitus.¹² MetS encompassing many underlying

dysfunctional mechanisms such as glucose intolerance, central obesity, hypertension, glucose intolerance, low serum HDL and hyper-triglyceridemia.¹³ In the present study the BMI levels of MetS patients was high when compare with healthy controls, clearly it indicates the central obesity of MetS component. Similarly, the hyper triglyceridemia and low HDL-cholesterol was observed in MetS cases. Recently, a comprehensive review study has described the association between fetuin-A and obesity with its complications.¹⁴ This atherogenic lipid profile can primes to risk factor of type 2 diabetes and cardiovascular disease.

In the present study we have observed the fasting glucose and insulin levels were elevated along with fetuin-A in MetS patients when compared with healthy controls. In addition to these the insulin resistance surrogate marker HOMA-IR was increased in MetS cases. Previously animal and human studies have been reported that fetuin-A relationship with insulin resistance.¹⁵⁻¹⁷ Earlier studies hypothesized that fetuin-A interferes with insulin action at peripheral tissues by inhibitory effect on insulin receptor.^{18,19} It is believed that insulin resistance is underlying mechanism to MetS phenotypes. In the present study, our results also support that fetuin-A may directly promote the MetS through mediating the insulin resistance.

Among the components of MetS, in the current study we have observed strong association of fetuin-A with fasting glucose, insulin and triglycerides. Several hepatokines secreted by the liver, including fetuin-A, have recently been shown to play a key role in the maintenance of whole-body energy homeostasis by controlling glucose and lipid metabolism.^{20,21} A systematic study and meta-analysis of observational research on the relationship between circulating fetuin-A and type-2 diabetes risk found that fetuin-A plays a function in the disorder of glucose and

lipid metabolism in diabetic humans.²² As prominent features of MetS shares with type-2 diabetes, the current study results similarly support that fetuin-A may play a role in MetS patients with glucose and lipid abnormalities. Recently, Pan et al studied a systematic review and meta-analysis reported on fetuin-A in MetS recommended that fetuin-A can be early diagnosis indicator.¹¹ In our study, ROC curve analysis was performed for fetuin-A cut-off value to predict MetS cases, it was observed that at cut-off 173.8, fetuin-A could distinguish the healthy controls from MetS cases with 68% sensitivity, 69% specificity (AUC 0.76, and 95% CI: 0.65-0.86).

Limitations

First, small sample size. It could be better results for prediction of MetS with larger sample size. Second, the data about life style habits such as alcohol drinking and vegetable intake which might be confounding variables in the development of MetS was not collected.

CONCLUSION

We found that serum fetuin-A levels were strongly and independently associated with MetS. Our finding suggests that fetuin-A could be used as a useful marker in clinical practice in the future for the early diagnosis and discovery of novel targets for pharmacological interventions to MetS.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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