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Original Research Article

Fetuin A levels and its correlation with lipid profile in type 2 diabetes mellitus patients

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM), is a chronic metabolic disorder. Due to its complex pathophysiology, several biomarkers have been studied for identifying its complications. Fetuin A has been proposed to be linked with insulin resistance and its comorbidities and may be helpful in understanding the pathophysiology of the disease condition. Therefore, the present study is aimed to evaluate the Fetuin A levels in Type 2 diabetes mellitus patients and its correlation with blood sugar, renal profile and lipid profile.

Materials and Methods: This prospective study was conducted in SRVS Government Medical College, Shivpuri, Madhya Pradesh, India. In this study, 90 T2DM patients as cases and 90 healthy subjects as controls were recruited. Demographic details, physical and clinical examination were done. Patients with cardiovascular diseases, thyroid diseases, liver disease, pregnant women were excluded from the study. Under aseptic conditions, 5 ml of fasting venous blood samples were collected, centrifuged to obtain serum sample. The obtained serum sample was used for the estimation of fasting glucose, post-prandial glucose, renal profile (serum urea, creatinine and uric acid), lipid profile (serum total cholesterol, triglycerides, HDLC, LDLC and VLDL) using commercially available autoanalyzer kits. Serum Fetuin A levels were estimated by using ELISA method. Whole blood sample was used for the estimation of HbA1c. The results were represented as Mean±SD. and percentage. Spearman's correlation was applied. The p value <0.05 considered statistically significant.

Results: In this study, in T2DM cases, males were 51 and females were 39 and in controls, males were 50 and females were 40. In the current study, age (63.8±5.7 years), BMI (26.2±1.6 kg/m^2) SBP (130.8±13.2 mmHg), DBP (90.6±12.7 mmHg), FBS (158.7±14.5 mg/dl), PPBS (228.5±31.8 mg/dl), HbA1c (7.8±0.7 %), Urea (32.1±9.4 mg/dl), Creatinine (1.0±0.1 mg/dl), Uric acid (6.2±2.8 mg/dl), total cholesterol (228.4±33.0 mg/dl), triglycerides (160.0±15.2 mg/dl), LDLC (165.6±33.6 mg/dl), VLDL (32.0±3.0 mg/dl) and Fetuin A (363.9±126.2 micg/ml) levels were significantly increased and HDLC (30.7±3.9 mg/dl) levels were reduced in T2DM cases than the healthy controls. Fetuin A level were significantly positively correlated with FBS (r=0.686), PPBS (r=0.656), HbA1c (r=0.694), Urea (r=0.342), Creatinine (r=0.564), Uric Acid (r=0.588), Total Cholesterol (r=0.700), Triglycerides (r=0.405), LDLC (r=0.728), and VLDL (r=0.528) and negatively correlated with HDLC (-0.681).

Conclusion: Elevated fetuin A and atherogenic lipid profile may be a risk for cardiometabolic diseases.

1. Introduction

Type 2 Diabetes mellitus (T2DM), commonly described as a metabolic disorder characterised by hyperglycaemia

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due to defective insulin secretion, action or both. T2DM is a major public health problem globally. According to International Diabetes Federation (IDF), estimates that the global prevalence of diabetes mellitus projected to increase to 643 million by 2030 and 783 million by 2045. The growing prevalence of the disease has an impact on social and economic status. India has an estimated 77 million people with diabetes. This may project to increase 134 million by 2045.[1,2]

Due to its complex pathophysiology, several biomarkers have been studied for identifying its vascular complications. However, many of these biomarkers were related to inflammation, metabolic or procoagulant. However, these biomarkers display huge variations in hazard prediction depending on disease severity.[3]

Fetuin - A has been proposed to be linked with insulin resistance and its comorbidities and may be helpful in understanding the pathophysiology of the disease condition.[4] Fetuin-A, multifunctional glycoprotein. It also referred to as α-2 Heremans Schmid glycoprotein (AHSG), secreted mainly from the hepatocytes. However, recently, a few studies have reported that the expression and secretion of Fetuin from adipose tissue. Therefore, Fetuin - A may be considered as hepatockine & adipokine.[5,6] Fetuin-A gene is located on the chromosome 3q27, which is also linked with T2DM and cardiometabolic disorders.[7] Fetuin - A plays a significant role in safety from vascular calcification by solubilizing the calcium and phosphorous in serum. In addition to this, it also plays a critical role in inhibition of insulin receptor substrate-1 (IRS-1) in muscle, liver, and initiates a low-grade inflammation, which causes insulin resistance.[8]

Studies have reported that Fetuin - A may be associated with metabolism of glucose, lipids and insulin resistance, including (a) inhibition of insulin actions through inhibition of insulin receptor tyrosine kinase and glucose transporter 4; (b) in combination with saturated fatty acids it may stimulate inflammation through the Toll-like receptor 4 (TLR4), results in IR;[9,10] (c) the expression of mRNA/ protein of Fetuin-A are high in ob/ob mice;[11] (d) impaired adipocyte function leads to Insulin Resistance (IR);[12] (e) high expression of Fetuin-A is linked with endoplasmic reticulum (ER) stress, which may lead IR.[13]

However, it has been observed that polymorphisms in Fetuin-A gene were associated with T2DM.[14] Serum Fetuin - A levels were associated with metabolic syndrome, T2DM and blood pressure.[15,16] Fetuin-A acts by blocking the insulin from attaching to its receptors, creates a pathway and causes insulin resistance concerned with T2DM pathophysiology.[17] Therefore, the present study is aimed to evaluate the Fetuin - A levels in Type 2 diabetes mellitus patients and its correlation with blood sugar, renal profile and lipid profile.

2. Materials and Methods

This prospective study was conducted in SRVS Government Medical College, Shivpuri - 473551, Madhya Pradesh, India. In this study, a total of 180 subjects were involved, among them 90 were T2DM patients as cases and 90 healthy subjects as controls. This study was approved by the institutional ethics committee and informed consent was obtained from all the study subjects. Demographic details, physical and clinical examination were done for all the study subjects. Patients with cardiovascular diseases, thyroid diseases, liver disease, pregnant women were excluded from the study.

Under aseptic conditions, 5 ml of fasting venous blood samples were collected from each study participant and aliquoted into plain (3ml) and EDTA (2 ml) tubes and allowed to stand for 1 hr and centrifuged at 3000 rpm for 10 minutes at 4° C to obtain the clear serum sample. The obtained serum sample was used for the estimation of fasting and post-prandial glucose (GOD-POD), renal profile [serum urea (Urease), creatinine (Jaffe kinetic) and uric acid (Uricase)], lipid profile [serum total cholesterol (CHOD-POD), triglycerides (GPO-POD), HDLC (Direct method), LDLC (calculation) and VLDL (calculation)] using commercially available autoanalyzer kits. Serum Fetuin-A levels were estimated by using ELISA method. Whole blood sample was used for the estimation of HbA1c (Immunoturbidimetry). Height and weight were recorded and Body Mass Index (BMI) was calculated.

2.1. Statistical analysis

The results were represented in Mean±SD. Categorical variables were represented in percentage. Spearman's correlation was applied. Data analysis was done by using SPSS version 22. The p value <0.05 considered statistically significant.

3. Results

In this study, 90 T2DM patients as cases and 90 healthy subjects as controls were involved to assess the fetuin A levels and to correlate with blood glucose, renal profile and lipid profile parameters. In this study, in T2DM cases, males were 51 and females were 39 and in controls, males were 50 and females were 40. In the current study, age (63.8±5.7 years), BMI (26.2±1.6 kg/m^2) SBP (130.8±13.2 mmHg), DBP (90.6±12.7 mmHg), FBS (158.7±14.5 mg/dl), PPBS (228.5±31.8 mg/dl), HbA1c (7.8±0.7 %), Urea (32.1±9.4 mg/dl), Creatinine (1.0±0.1 mg/dl), Uric acid (6.2±2.8 mg/dl), total cholesterol (228.4±33.0 mg/dl), triglycerides (160.0±15.2 mg/dl), LDLC (165.6±33.6 mg/dl), VLDL (32.0±3.0 mg/dl) and Fetuin A (363.9±126.2 micg/ml) levels were significantly increased and HDLC (30.7±3.9 mg/dl) levels were significantly reduced in T2DM cases compared to healthy controls as shown in Table 1.

Table 1: Comparison of demographic and biochemical parameters betweenT2DM cases and healthy controls

Parameters	T2DM Cases (n=90)	Healthy Controls (n=90)	P Value
Age (years)	63.8±5.7	51.0±3.7	<0.001
Male	51 (56.6%)	50 (55.5%)	-
Female	39 (43.3%)	40 (44.4%)	-
BMI (kg/m^2)	26.2±1.6	22.0±1.5	<0.001
Systolic blood pressure (SBP) (mmHg)	130.8±13.2	114.9±5.0	<0.001
Diastolic blood pressure (DBP) (mmHg)	90.6±12.7	75.0±5.0	<0.001
Fasting blood sugar (mg/dl)	158.7±14.5	97.5±8.2	<0.001
Post-Prandial blood sugar (mg/dl)	228.5±31.8	133.5±5.1	<0.001
HbA1c (%)	7.8±0.7	5.1±0.41	<0.001
Serum Urea (mg/dl)	32.1±9.4	28.4±6.6	<0.001
Serum Creatinine (mg/dl)	1.0±0.1	0.7±0.1	<0.001
Serum Uric Acid (mg/dl)	6.2±2.8	4.8±0.6	<0.001
Serum Total Cholesterol (mg/dl)	228.4±33.0	171.7±8.4	<0.001
Serum Triglycerides (mg/dl)	160.0±15.2	145.0±4.8	<0.001
Serum HDLC (mg/dl)	30.7±3.9	43.7±4.5	<0.001
Serum LDLC (mg/dl)	165.6±33.6	98.5±7.1	<0.001
Serum VLDL (mg/dl)	32.0±3.0	29.0±0.9	<0.001
Serum Fetuin – A (micg/ml)	363.9±126.2	256.8±92.0	<0.001

P<0.05 statically significant

Table 2: Correlation of fetuin A with other study parameters

Parameters	r- value	P value
FBS	0.686**	0.000
PPBS	0.656**	0.000
HbA1c	0.694**	0.000
Serum Urea	0.342**	0.000
Serum Creatinine	0.564**	0.000
Serum Uric Acid	0.588**	0.000
Serum Total Cholesterol	0.700**	0.000
Serum TGL	0.405**	0.000
Serum HDLC	-0.681**	0.000
Serum LDLC	0.728**	0.000
Serum VLDLC	0.528**	0.000

**. Correlation is significant at the 0.01 level (2-tailed).

Fetuin A level were positively correlated with FBS (r=0.686), PPBS (r=0.656), HbA1c (r=0.694), Urea (r=0.342), Creatinine (r=0.564), Uric Acid (r=0.588), Total Cholesterol (r=0.700), Triglycerides (r=0.405), LDLC (r=0.728), and VLDL (r=0.528) and HDLC (-0.681) levels were negatively correlated as shown in Table 2.

4. Discussion

Prevalence of T2DM is increasing globally. The current study is designed to assess the Fetuin A levels in T2DM patients in comparison with healthy controls and its correlation with blood sugar, renal profile and lipid profile parameters. In this study, we observed significant elevation in fetuin A levels among T2DM cases than the healthy controls and found a significant positive correlation with blood sugar, renal profile and lipid profile parameters except for HDLC, which was negative correlation.

In this study, Fetuin A levels were positively correlated with BMI. This finding was supported by Ismail et al. reported an association between fetuin-A levels and BMI in obese children.[18] In another study by Chatterjee et al. reported a positive correlation of Fetuin A with BMI, WHR, blood pressure.[19] In this study, Fetuin A levels were positively correlated with blood pressure. These findings were similar with the study conducted by Chung et al. reported that serum Fetuin-A levels showed a significant positive correlation with systolic blood pressure.[20] Elevated blood pressure may be explained by damaging of endothelial normal function and platelets is associated with hyperglycaemia, dyslipidaemia, insulin resistance, which may lead to inflammation and vasospasm.[21]

Along with diabetic markers such as FBS, PPBS, and HbA1c, fetuin A level were also increased in T2DM compared to controls. These findings were supported by Guo et al study, they reported that significantly elevated levels of circulating fetuin-A and were associated with the risk of T2DM.[22]

Similarly, another study by Pinnaduwage et al. reported that circulating hepatic biomarkers, especially Fetuin-A, track with changes in insulin sensitivity and β-cell function, indicating its involvement in disease pathology in prediction of diabetic risk.[23] Yet, another study by Sujana et al. reported that elevated Fetuin-A levels are associated with T2DM risk.[10] Ou et al. study reported that Fetuin-A may further aggravate increased arterial stiffness in diabetic patients.[24]

In contrast to above studies, Eleftheriadou et al. documented lower plasma fetuin-A levels in T2DM cases than healthy controls.[25] Similarly, yet another study by Roos et al. also reported that lower fetuin-A levels were associated with macrovascular complications in Diabetes.[26] In this study, renal profile parameters were also showed significant increase and were correlated with Fetuin A.

In this study, significant elevation in the mean levels of lipid profile parameters such as total cholesterol, triglycerides, LDLC, VLDL in T2DM cases than the controls and positive correlation was observed between fetuin A and lipid profile parameters except HDLC, it showed negative correlation. According to the modified criteria for metabolic syndrome developed by the NCEP-ATP III and IDF, triglycerides, HDL, and blood pressure were correlated with fetuin-A levels.[27] These findings were supported by a study conducted by Erdmann J et al. reported a positive correlation of Fetuin-A with triglycerides and blood pressure and negative correlation with HDL in prepubertal subjects. Association between fetuin-A and cardiometabolic risk factors also documented in adults.[28]

In children and adolescents, it has been reported that increased fetuin-A levels are risk factor for cardiometabolic diseases. Because fetuin-A is a produced in the liver, the risk factors for cardiovascular and metabolic diseases that are related to fetuin-A, associated with increased IR rather than obesity or overweight. However, fetuin-A plays an independent role in cardiovascular and metabolic disease risk.[29]

In this study, significant correlation of fetuin A with atherogenic lipid profile was observed. In a study conducted by Joachim H. Ix et al. proposed a hypothesis that insulin receptor inhibition by fetuin-A may results in lipolysis and release of free fatty acids from adipose tissue. This may, in turn, causes increased production of apolipoprotein B–containing VLDL. Furthermore, hypertriglyceridemia may result in low cholesterol content of HDL, which may increase HDL clearance from the circulation, thereby potentially leading to the atherogenic lipid profile.[30]

5. Conclusion

The present study results may conclude that fetuin- A levels were significantly high in patients with T2DM and its levels were significantly correlated with FBS, PPBS, HbA1c, renal profile, and atherogenic lipid profile parameters. Elevated fetuin A and atherogenic lipid profile may be a risk for cardiometabolic diseases. Further studies with large sample size are recommended.

6. Conflict of Interest

There are no conflicts of interest.

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