Serum Fetuin-A Levels in Type 2 Diabetes Patients with Early Diabetic Nephropathy: It's Relation to Diabetes Control

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Abstract: Background and objective: Fetuin-A is a circulating calcium-regulatory glycoprotein that inhibits vascular calcification. In the present study, serum fetuin-A was studied as a novel risk factor for the development of diabetic nephropathy and the relation between its levels with the state of diabetes control. Patients and Methods: 50 patients with type 2 diabetes mellitus (T2DM) and early diabetic nephropathy, 25 patients of them have well controlled diabetes on treatment (the first group), the other 25 patients have uncontrolled diabetes (the second group), and another 25 healthy volunteers (control group)) were enrolled in this cross sectional study. Serum fetuin-A, Fasting plasma glucose (FP glucose), glycoselated hemoglobin A1c, lipid profile (total cholesterol,HDL and triglycerides), Serum creatinine, Glomerular filtration rate (GFR), Albumin excretion in urine were measured. Results: There was a significant reduction in Serum fetuin-A levels in controlled diabetic patients (314±66.8) and uncontrolled diabetic patients (252.4±55.6) compared to control group (478.6±74.4). A significant decrease was also detected in uncontrolled diabetic patients when compared to controlled diabetic patients (P<0.001). A strong inverse correlation was found between serum fetuin-A and each of F P glucose, glycoselated hemoglobin (HbA1c), serum creatinine, and urinary albumin excretion (r = -0.52, -0.55, -0.61, and -0.56 respectively; P < 0.001 for each). Whereas; GFR was significantly positively associated with serum fetuin-A levels (r = 0.53, P<0.001). Conclusion: The results of this study demonstrate that diabetic nephropathy, especially with uncontrolled diabetes, is linked to low serum fetuin-A levels which represents a novel risk factor for the development of vascular complications. This factor could be responsible for the development and progression of accelerated nephropathy especially with uncontrolled diabetes.

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1. Introduction:

Various biomarkers have been studied for identification of type 2 diabetes patients at micro- and macrovascular risk. Most of these markers are inflammatory, metabolic or procoagulant molecules indicating an unfavorable metabolic and vascular status in patients with type 2 diabetes [1]. However, the different biomarkers show large variations in risk prediction depending on metabolic status and disease severity of the study groups [2,3]. Recently published data imply, that most novel biomarkers do not improve risk prediction when added to models based on conventional risk scores [4] Yet, associations of novel biomarkers such as fetuin-A with metabolic markers or complications do help to understand their role in the pathophysiology of vascular disease.

Fetuin-A, a circulating calcium-regulatory glycoprotein that inhibits vascular calcification, is predominantly synthesized in liver. It is secreted into the blood stream and deposited as a noncollagenous protein in mineralized bones and teeth. During fetal life, there is high serum concentration of fetuin-A. Its level declines following infection, acute or chronic inflammatory states and malignancy [5,6]. Low serum fetuin-A levels have been reported in chronic renal disease and dialysis patients and is associated with inflammation and outcome [7,8]. Recent data have shown a relationship between vascular calcification and endothelial dysfunction in vascular disease [9]. Therefore, low serum fetuin-A level could be one of the contributing factors for the development of endothelial dysfunction in chronic renal disease patients.

So far, there is few data available for associations of fetuin-A with parameters of microvascular disease in diabetes. To clarify the relation between fetuin-A and microvascular complications in patients with type 2 diabetes and early diabetic nephropathy, we studied its associations with albuminuria and parameters of renal function. In addition, the state of diabetes control of these patients was assessed by quantification of the

glycoselated hemoglobin A1c and its association with fetuin-A levels was assessed.

2. Methods

Study population and data collection

This study was carried out in Internal Medicine and Clinical Pathology departments, faculty of medicine, Zagazig University. This cross sectional study was conducted from January 2010 to January 2011.

This study included 50 patients with type 2 diabetes mellitus (T2DM) and early diabetic nephropathy who were recruited from the outpatient clinics of Endocrinology and Diabetes at Zagazig University Hospital and referred to the diabetes control for specialist treatment. The selection of patient groups was as follows:

25 patients were selected to have well controlled diabetes on treatment (First group): They were 13 males & 12 females, having a mean age of 53.76 ± 6.0 years, and a mean HbA1c of 6.2 ± 0.7.

25 patients were selected to have uncontrolled diabetes on treatment (second group): They were 13 males & 12females, having a mean age of 55 ± 6.2 years, and a mean HbA1c of 11 ± 2.1.

Another age and sex matched 25 healthy volunteers were chosen as a control group.

Inclusion criteria: patients with T2DM who had to have a documented history of albuminuria in at least two separate urine samples (urinary albumin > 20 mg/L as suggested by current German and international guidelines for the diagnosis of diabetic nephropathy) [10].

Exclusion criteria: We excluded patients with malignant neoplasms, severe infectious disease, severe congestive heart failure, type 1 diabetes and other renal disease by urinary sediments and medical records (macroscopic hematuria, abnormal sediment, urinary tract infection and past history of glomerulonephritis or nephro-ureterolithiasis).

All patients were submitted to full clinical assessment including history taking and through clinical examination including blood pressure measurements (systolic and diastolic) and assessment of body mass index (BMI). In all individuals, 24-h urine samples were collected and the albumin excretion rate in 24 hours is estimated. The study complied with the Declaration of Helsinki, and all subjects gave informed consent to participate in this study.

Clinical chemistry

Blood was drawn in a fasting state under sterilized conditions and stored at -80°C until analysis. The following investigations were done:

Fasting plasma glucose (FPglucose) was measured by a glucose oxidase method. Triglyceride (TG), total cholesterol, and high density lipoprotein cholesterol (HDL) levels were quantified by using ADVIA 1650 auto analyzer (Siemens Medical Solutions Diagnostic. USA). Glycoselated hemoglobin (Hb A1c) was estimated by ion exchange resin chromatography using Stanbio Glycohemoglobin.

Glomerular filtration rate is estimated from the Modification of Diet in Renal Disease (MDRD) formula [11] as follows: MDRD formula = 186 X [serum creatinine (mg/dl)]$^{-1.154}$ X [age]$^{-0.203}$ X [0.742 if patient is female] X [1.21 if patient is African-American], which is used for statistical evaluation of renal function.

Albumin excretion rate (AER) was assessed and performed in 24-h urinary collections. For collection of the urine sample, a 3-l plastic container was used, and the volume of urine was measured to the nearest 50 ml. Albumin levels were determined by turbidimetry (Siemens Healthcare Diagnostics, Eschborn, Germany). AER was expressed as milligrams per 24 h.

Serum fetuin-A was measured in duplicates by an ELISA (Epitope Diagnostics, Inc., San Diego, USA) The intra- and interassay variations were 5.3 and 7.1%, respectively.

Statistical analyses

Statistical analyses of the results were performed using SPSS software version 15.0 (statistical package for social science, SPSS inc. Chicago, USA). Continuous variables were expressed as means± standard deviation (SD)**.** Comparison between two sets of patients was performed by independent t test, but more than two sets of patients were compared by one-way ANOVA**.** The Kruskal-Wallis (KW) test was applied to compare the values of HbA1c, F P glucose and Albumin in urine (non normal distributed variables) among the three groups of the study. Pearson correlation coefficient 'r' was used to describe the association between serum fetuin-A and the variables of interest. P values <0.05 were considered statistically significant.

3. Results:

Clinical and laboratory characteristics of all patients with diabetes mellitus and healthy control subjects and comparison between all groups are given in Table 1.

Table 1: Demographic, Ciinical and laboratory characteristics of the studied groups.

Parameter	Control group n=25	Controlled diabetic group n=25	Uncontrolled diabetic group n=25	F /X^2 / t	P
Age (y)	53.6 ± 6.1	53.76 ± 6.0	55 ± 6.2	0.4	0.6
Gender (M/F)	12(48%)/13(52%)	13(52%)/12(48%)	13(52%)/12(48%)	0.11	0.94
BMI (kg/m^2)	25.1 ± 4.1	26.8 ± 2.4	26.2 ± 3.2	1.6	0.2
Duration (y)		10.6± 4.9	10.56±4.9	0.02	0.97
Systolic B P (mmHg)	118.5±5.1	122.5±8.2	123.8±10.5	2.8	0.06
Diastolic B P(mmHg)	77.7±4.0	78.4±5.0	76.9±5.1	0.61	0.54
ACE therapy (n,%)		12 (48%)	13 (52%)	0.08	0.77
Insulin therapy (n,%)		14 (56%)	12 (48%)	0.32	0.67
HbA1c (%) X±SD Range Median	 5.4 ± 0.5 4.4 – 6.1 5.4	 6.2 ± 0.7 + 5.9 - 6.7 6.4	 11.0 ± 2.1 * 7.5 – 15.0 11	 KW 49.6	 <0.001**
F P glucose (mg/dl) X ± SD Range Median	 82.3 ±7.8 70 – 97 83	 92.2± 12.82 + 70 – 120 94	 127.3 ± 20.2 * 89 – 170 125	 KW 47.69	 <0.001**
Serum creatinine (mg/dl)	0.55 ± 0.12*	0.9 ± 0.18	0.95 ± 0.19	41.1	<0.001**
GFR (ml/min/1.73m^2)	126.4±14.6*	103.1±14.6	95.5±17.7	26.1	<0.001**
Serum albumin (gm/dl)	4.5± 0.3	4.4±0.3	4.4±0.35	0.27	0.75
Triglycerides (mg/dl)	119.2± 23.3*	160.2± 43.7	157.2± 49.4	7.99	<0.001**
Total cholesterol (mg/dl)	160.2±23.3 *	194.5±42.3	205 ±47.1	9.5	<0.001**
HDL (mg/dl)	52.5±9.7 *	45.9±7.0	42.7±8.1	8.94	<0.001**
Albumin excretion (mg/24h) X ± SD Range Median	 6.7± 3.1 2 – 13 6	 188.4± 114+ 40 – 450 160	 243± 140.5 * 56 – 560 247	 KW 50.13	 <0.001**
Serum fetuin-A (mg/L)	478.6±74.4	314± 66.8 +	252.4± 55.6*	78.3	<0.001**

**P is significant. KW, The Kruskal-Wallis test.
* Significance is present between this group and the other two groups.
+ Significance is present between controlled diabetics and control group.
BMI: Body mass index. HbA1c: Glycoselated hemoglobin. F P glucose: Fasting plasma glucose.
GFR: Glomerular filtration rate. HDL: high density lipoprotein.

There were no differences in age {P=0.6}, sex {P=0.94}, duration of diabetes {P=0.97}, body mass index (BMI) {P=0.2}, systolic blood pressure {P=0.06}, diastolic blood pressure {P=0.54}, and serum albumin {P=0.75} among all groups of the study. There was no differences in the percentage of diabetic patients on treatment by ACE or insulin therapy between the two groups of diabetes mellitus {P=0.77 and 0.67 respectively}.

Fasting plasma glucose levels were significantly higher in the uncontrolled diabetic group (127.3 ± 20.2) than in the controlled diabetic group (92.2± 12.82) and healthy control group (82.3 ±7.8) {p<0.001}, and also there was a significant increase in FP glucose in the controlled diabetic group as compared to healthy control group {p<0.001}.

Hemoglobin A1c (HbA1c) was significantly higher in the uncontrolled diabetic group (11.0 ± 2.1) than in the controlled diabetic group (6.2 ± 0.7) and healthy control group (5.4 ± 0.5) {p<0.001}, and also there was a significant increase in HbA1c in the controlled diabetic group as compared to healthy control group {p<0.001}.

Serum creatinine levels were significantly higher in both the uncontrolled diabetic group (0.95 ± 0.19) and controlled diabetic group (0.9 ± 0.18) than in the healthy control group (0.55 ± 0.12) {p<0.001}, there was no significant difference in Serum creatinine between the uncontrolled and controlled diabetic groups.

GFR levels were significantly lower in both the uncontrolled diabetic group (95.5±17.7) and controlled diabetic group (103.1±14.6) than in the healthy control group (126.4±14.6) {p<0.001}, there was no significant difference in GFR between the uncontrolled and controlled diabetic groups.

Albumin excretion in urine was significantly higher in the uncontrolled diabetic group (243±140.5) than in the controlled diabetic group (188.4±114) and healthy control group (6.7±3.1) {p<0.001}, and also

there was a significant increase in urinary Albumin excretion in the controlled diabetic group as compared to healthy control group {p<0.001}.

Triglyceride and cholesterol levels were significantly higher in both the uncontrolled diabetic group (157.2±49.4 and 205 ±47.1, respectively) and controlled diabetic group (160.2± 43.7 and 194.5± 42.3, respectively) than in the healthy control group (119.2±23.3 and 160.2±23.3 , respectively) {p<0.001}, there were no significant difference in triglyceride or cholesterol levels between the uncontrolled and controlled diabetic groups.

HDL levels were significantly lower in both the uncontrolled diabetic group (42.7±8.1) and controlled diabetic group (45.9±7.0) than healthy control group (52.5±9.7) {p<0.001}, there was no significant difference in HDL between the uncontrolled diabetic and controlled diabetic groups.

Serum fetuin-A levels were significantly lower in the uncontrolled diabetic group (252.4±55.6) and the controlled diabetic group (314±66.8) than in the healthy control group (478.6±74.4) {p<0.001}, and also there was a significant reduction in serum fetuin-A in uncontrolled diabetic group as compared to controlled diabetic group (p<0.001).

Table 2: Correlation between Serum fetuin and other Parameters of the study.

Parameter	Serum fetuin	
	r	P
Age	-0.09	> 0.05
Body mass index	0.001	> 0.05
Systolic blood pressure	-0.19	>0.05
Diastolic blood pressure	-0.03	>0.05
Duration of diabetes	0.02	>0.05
Glycoselated HbA1c	-0.55	<0.001*
Fasting plasma glucose	-0.52	<0.001*
Serum creatinine	-0.61	<0.001*
Serum albumin	0.06	>0.05
Triglycerides	-0.15	>0.05
Total cholesterol	-0.21	>0.05
high density lipoprotein	0.2	>0.05
Glomerular filtration rate	0.53	<0.001*
Albumin excretion in urine	-0.56	<0.001*

* Correlation is highly significant.

The overall mean serum level of fetuin-A was 348.36 ± 116.1 mg/L with a range of 170 to 620 mg/L. Correlation study revealed that each of HbA1c, FP glucose, serum creatinine and Albumin excretion were significantly and inversely associated with serum fetuin-A levels (r = -0.55, -0.52, -0.61, and -0.56 respectively; P < 0.001 for each), whereas; GFR was significantly positively associated with serum fetuin-A levels (r = 0.53, P<0.001). No other clinical or metabolic variable (as BMI, blood pressure, total cholesterol,HDL and triglyceride) was significantly correlated in these groups of diabetic patients with serum fetuin-A (P >0.05 in all, see table 2). The overall mean serum level of fetuin-A in male individuals was 347.5±126.5 mg/L, with no significant difference from that of female individuals (346.5 ± 107.6 mg/L, p = 0.97).

4. Discussion

The gene encoding fetuin-A is located on chromosome 3q27, the chromosomal region that was previously mapped as a type 2 diabetes and metabolic syndrome susceptibility locus (12). The aforementioned findings and the animal studies showing that fetuin-A induces insulin resistance (13-16) resulted in the view that fetuin-A is an interesting candidate involved in the pathophysiology of type 2 diabetes. Genetic analyses revealing that single nucleotide polymorphisms in the fetuin-A gene were associated with type 2 diabetes in cross-sectional studies (17) further corroborated this hypothesis. However, the role of fetuin-A in the natural history of type 2 diabetes still remained obscure. Fetuin-A, besides the placenta, is exclusively secreted from the liver (18). Expression of fetuin-A and plasma levels of the protein were found to be increased when there is fat accumulation in the liver (19,20) and circulating fetuin-A is increased in the metabolic syndrome (21), the condition that strongly associates with fatty liver (22). Moreover, fetuin-A complexes with calcium and phosphorus in the circulation and prevents the precipitation of these minerals in serum [23,24].

Fetuin-A is regarded as marker for vascular inflammation and as one of the most potent negative regulators of vascular ossification - calcification [25,26]. In animals lacking the fetuin-A gene, the aorta was found to be spared of calcification and fibrosis, whereas peripheral vessels in the skin and kidney showed evidence of extensive calcification, and the small artery involvement preceded the impairment of renal function [24,27].

In this study ,we evaluated the associations of parameters of microvascular disease in patients with T2DM and early diabetic nephropathy as the degree of albumin excretion and renal function(GFR and serum creatinine) with fetuin-A.

This study demonstrates that lower fetuin-A levels seem to be associated with microvascular complications in patients with early diabetic nephropathy disease in type 2 diabetes as evidenced by the significant inverse association between fetuin-A concentrations and the degree of 24 h urinary albumin excretion and also, the significant positive association between fetuin-A concentrations and GFR .

Furthermore, we could show that there is a link between fetuin-A serum levels and the state of diabetes control which was determined by the inverse association between fetuin-A concentrations and HbA1c .

In addition, fetuin-A levels do not correlate with some clinical and metabolic parameters as BMI, blood pressure, total cholesterol, HDL and triglyceride in our type 2 diabetic patients with early diabetic nephropathy with or without hyperglycemia.

The data presented herein allows to speculate, that fetuin-A could play a role in the development of early microvascular disease (especially nephropathy) in type 2 diabetes, yet possible mechanisms remain unclear. In line with this hypothesis, Eraso et al. showed that circulating fetuin-A was lower in 38 subjects with type 2 diabetes and an ankle/brachial index (ABI) < 0.9, compared with 700 diabetes controls [28]. Also Roos et al .assessed ABI as a paramerter of microvascular disease and demonstrated that type 2 diabetic patients with an ABI <0.9 had lower fetuin-A levels than patients with an ABI 0.9-1.3 or > 1.3 and that fetuin-A was significantly associated with ABI. Moreover, Roos et al. found that lower fetuin-A levels seem to be associated with prevalent macrovascular disease (as coronary artery disease, stroke and peripheral artery disease) in type 2 diabetes. But in contrast to our results, they showed also that fetuin-A serum levels are not associated with microvascular complications (24 h urinary albumin excretion) in patients with early diabetic nephropathy. In addition, they agree with us to some extent in that fetuin-A levels do not correlate with metabolic parameters in their type 2 diabetes patients with prevalent late complications [29].

Again, a recently published study in patients without diabetes and renal impairment demonstrated decreased fetuin-A serum levels in patients suffering from advanced three-vessel disease compared with those without stenosis [30]. These finding go in line with our assumption of reduced fetuin-A serum levels in patients with diabetic nephropathy.

Reviewing the existing data as well as the results obtained in this study, it may be assumed that fetuin-A levels are lower in type 2 diabetes patients with early diabetic nephropathy especially those with uncontrolled diabetes.

Our results are in contrast to findings in several cross-sectional studies which showed an association of high fetuin-A levels with impaired glucose tolerance, metabolic syndrome and an atherogenic lipid profile (high low-density lipoprotein, high triglyceride concentrations and low HDL concentrations) [31,32] and the positive association of Plasma fetuin-A levels with the risk of type 2 diabetes [33].

We recognize the limitations of the present study. Our approach is limited by the small samples size. Therefore, especially the data for associations with microvascular disease and renal function in type 2 diabetes will have to be reproduced in larger groups.

5. Conclusions

In this study, low plasma fetuin-A levels predict microvascular complications in type 2 diabetes with early diabetic nephropathy and also there are associations of fetuin-A with hyperglycemia in these patients.

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