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Research Article

Serum fetuin-A in diabetic and nondiabetic hemodialysis patients

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Abstract

Background: Diabetes mellitus is a major public health issue affecting millions of people and it is associated with diabetic kidney disease which could be developed into dialysis in many cases and early prediction will help to prevent its hazards efficiently. The aim of the study is to explore the effect and assess the role of fetuin-A in diabetic and nondiabetic patients on hemodialysis. **Methods:** This is a case-control study that was performed at the Internal Medicine Department, Minia University Hospital during the period from June 2021 to February 2022. The study included a total of 45 subjects who were classified to 3 groups (n=15 per each); group (I) included healthy control subjects, group (II), included non-diabetic patients on hemodialysis (HD group) and group (III) included diabetic patients on hemodialysis (DM+HD group). Serum Fetuin-A was measured by ELISA before and after hemodialysis. **Results:** There were significant differences among the three studied groups in Fetuin-A level. DM patients group (group II and group III) had significantly higher Fetuin-A level compared to the control group ($p< 0.01$). There were significant differences between Group II and III in Fetuin-A before dialysis and the same trend of results was found after dialysis. Fetuin-A level was significantly decreased after dialysis compared to pre-dialysis values in group II and III ($p< 0.01$). Also, the higher Fetuin-A levels were associated with HTN and cardiac affected cases. There were a highly significant positive correlation between Fetuin-A level and age, SBP, RBS, HbA1C, urea, createnine and T. cholesterol ($p<0.01$). **Conclusion:** Fetuin-A was significantly higher in diabetic patients on hemodialysis compared to non-diabetic patients on hemodialysis and the normal healthy subjects. The elevated circulating concentrations of Fetuin-A may be a risk factor for conditions such as type 2 diabetes mellitus and impairment of kidney function

Keywords*:* Fetuin-A, Diabetes mellitus, Hemodialysis.

Introduction

Diabetes mellitus (DM) is a metabolic disease described by chronic hyperglycemia as a consequence of defects in insulin action, secretion, or both, it is a major public health problem affecting millions of people globally and there are massive complications associated with it, such as nephropathy, neuropathy, cardiovascular complications and retinopathy [(1)]. Diabetic kidney disease occurs in diabetic patients and reduced kidney function that can be from many diverse causes and it has been estimated that about 10-30% of type 1 DM and 15- 40% of type 2 DM patients suffer from diabetic kidney disease [(2)].

Biochemical markers have a vital role in accurate diagnosis and also for assessing risk and adopting therapy that improve clinical outcome. Fetuin-A is a hepatically synthesized 62-kDa glycoprotein belongs to the cystatin family of the proteinase inhibitors, it inhibits insulin receptor tyrosine kinase activity and it is directly associated with insulin resistance and

dyslipidaemia [3]. Fetuin-A increased in insulin resistance and it could be an independent predictor of type 2 DM [4]. Some studies reported that elevated circulating levels of fetuin-A is associated with impaired insulin sensitivity that leads to the development of insulin resistance and related comorbidities such as hypertriglyceridemia, obesity, impaired glucose tolerance, T2DM, NAFLD, and early-stage chronic kidney disease [5, 6]. On the other hand, some studies reported that dialysis patients have relatively low circulating fetuin-A levels [7, 8]. This study attempts to explore the effect and assesses the role of fetuin-A in diabetic and nondiabetic patients on hemodialysis.

Patients and Methods

This is a case-control control trial that was performed at the Internal Medicine Department, Minia University Hospital during the period from June 2021 to February 2022. The study included a total of 45 subjects who were classified to group (I) included 15 healthy subjects (non-diabetic and not on hemodialysis) served as control group (Control group), group (II), included 15 non-diabetic patients on hemodialysis (HD group) and group (III) included 15 diabetic patients on hemodialysis (DM+HD group).

Adult subjects (Age 20-60 year) of both genders were included. Exclusion criteria were; patients with chronic liver diseases, autoimmune diseases and those who receive drugs that increase blood sugar eg. corticosteroids. Concerning laboratory investigations, random blood sugar, HbA1C, urine analysis, blood urea and creatinine and lipid profile were determined using commercial kits. Serum Fetuin-A was measured in samples by Sandwich ELISA Detection method using the kits of SinoGeneClon Biotech Company LTS (HangZhou, China) [9]. Serum Fetuin-A was measured before and after hemodialysis for group II and III.

Ethical considerations: The study protocol and all procedures were approved by the ethical committee of the Minia Faculty of medicine. A verbal consent was taken from patients before getting them involved in study. The steps, the aims, the potential benefits and hazards, all were discussed with the patients

Statistical analysis

Statistical Package for Social Science (SPSS) version 21 [10] was used. Results are expressed as means ± SD for quantitative data and by No. (%) for qualitative data. Analyses were done for quantitative variables using one way ANOVA test for comparison between three groups and post Hoc Duncan's correction between each two groups. However, Chi square test was used for qualitative data between groups. Correlation between two quantitative variables was done by using Pearson's correlation coefficient and for non-parametric variables using Spearman's rho correlation test. Probability level (P. value) was assumed significant if < 0.05 and highly significant if < 0.01.

Results

No significant differences were noticed among groups regarding sex (p=0.70), BMI (p=0.98) and duration of dialysis (p=0.92) however, group (III) had significantly higher number of hypertensive and cardiac cases (Table, 1). There were significant differences between groups regarding SBP. While, no significant differences were noticed among groups regarding DBP (p=0.18) and heart rate (p=0.61). Dialysis patients groups (group II and III) had significantly higher pallor cases compared to the control group. Both random blood sugar and HbA1C are significantly higher DM+HD group (group III) compared to the other two groups (p<0.01. Dialysis patients groups had significantly higher both urea and createnine compared to the control group. There were significant differences between the two dialysis groups in total cholesterol compared to the control group (Table, 2).

Regarding Fetuin-A results (before dialysis) (Table, 2), there were significant differences among the three studied groups in Fetuin-A (the highest level was in DM+HD group, 92.5 ± 10.6 mg/l followed by HD group, 77.9 ± 15.4 mg/l however the lowest level was noticed in the control group 58.7 ± 13.6 mg/l, p< 0.01). Also, the results showed that patients group (group II and group III) had significantly higher Fetuin-A level compared to the control group (p< 0.01). In addition, the results showed that there were significant differences between the two groups in Fetuin-A before dialysis (92.5 ± 10.6 mg/l in DM+HD group vs. 77.9 ± 15.4 mg/l in HD group, p< 0.01). Also, the same

trend of results was found after dialysis, DM+HD group had significantly higher Fetuin-A level compared to HD group (67.8 ± 11.2 vs. 53.7 ± 13.6 mg/l), (Table, 2). Also, the results showed that Fetuin-A level was significantly decreased after dialysis compared to pre-dialysis values in group II and III (p< 0.01) (Figure, 1). Also, the results showed that both HTN cases and cardiac cases had significantly higher Fetuin-A level compared to normal cases (p<0.01), (Figure, 2).

The results of the correlation between Fetuin-A level (pre-dialysis) and different clinical and laboratory parameters in all included patients (n = 45) revealed that there were a highly significant positive correlation between Fetuin-A level and age, SBP, RBS, HbA1C, urea, createnine and T. cholesterol (all p<0.01), (Table, 3).

Table (1): Comparison between groups regarding demographic and baseline data

Variable	Group (I) Control (n = 15)	Group (II) HD group (n = 15)	Group (III) DM+HD (n = 15)	P. value (Sig.)
Age (years)	34.1^{A} ± 11.3	44.7^{B} ± 9.7	51.0^{B} ± 6.6	**<0.01****
Sex (Male/female)	7/8	7/8	9/6	0.70^{NS}
BMI (kg/m^2)	25.5 ± 4.1	25.3 ± 3.8	25.3 ± 3.2	0.98^{NS}
HTN (+ve)	0^{B}	4 (26.7%)^{B}	10 (66.7%)^{A}	**<0.01****
Cardiac (+ve)	0^{B}	2 (13.3%)^{B}	8 (53.3)^{A}	**<0.01****
Duration of dialysis	-	4.5	3.75	0.92^{NS}

NS Not significant , ** Significant (p<0.01). $^{A, B}$ Means in the same row (between groups) with different superscript letters are significantly different

Table (2): Comparison between groups regarding clinical and laboratory data

Variable	Group (I) Control (n = 15)	Group (II) HD group (n = 15)	Group (III) DM+HD (n = 15)	P. value (Sig.)
SBP (mm Hg)	113.3^{B} ± 11.6	121.7^{AB} ± 19.2	132.3^{A} ± 20.1	**0.02***
DBP (mm Hg)	73.3 ± 10.8	77.0 ± 11.1	80.7 ± 10.3	0.18^{NS}
Heart rate	81.4 ± 10.3	85.6 ± 8.6	84.3 ± 15.1	0.61^{NS}
Body temperature (C^{o})	37.3^{A} ± 0.52	36.7^{B} ± 0.40	36.9^{B} ± 0.27	**<0.01****
Pallor (+ve)	3 (20.0%)^{B}	11 (73.3%)^{A}	11 (73.3%)^{A}	**<0.01****
RBS (mg/dl)	104.4^{B} ± 22.6	114.5^{B} ± 13.6	233.7^{A} ± 35.6	**<0.01****
HbA1C (%)	5.34^{B} ± 0.37	5.65^{B} ± 0.23	7.91^{A} ± 0.96	**<0.01****
Urea (mg/dl)	32.2^{B} ± 13.8	135.5^{A} ± 7.1	134.1^{A} ± 31.0	**<0.01****
Creatinine (mg/dl)	0.97^{B} ± 0.13	5.34^{A} ± 1.603	5.39^{A} ± 1.54	**<0.01****
T. cholesterol (mg/dL)	168.7^{B} ± 21.7	196.1^{A} ± 29.7	203.3^{A} ± 30.6	**<0.01****
Triglyceride (mg/dL)	108.9^{B} ± 24.6	127.8^{B} ± 25.7	193.1^{A} ± 29.8	**<0.01****
Fetuin-A (mg/l)	58.7^{C} ± 13.6	77.9^{B} ± 15.4	92.5^{A} ± 10.6	**<0.01****

NS Not significant * Significant (p<0.05). ** Significant (p<0.01).
$^{A, B, C}$ Means in the same row (between groups) with different superscript letters are significantly different

Table (3): Correlation between Fetuin-A level (pre dialysis) and different clinical and laboratory parameters in all included patients (n = 45)

Correlations		(*r*) Correlation coefficient	P. value (Sig.)
Fetuin-A level	**Age**	0.53	**<0.01****
	BMI	0.22	0.14^{NS}
	SBP	0.30	**0.03***
	RBS	0.57	**<0.01****
	HbA1C	0.54	**<0.01****
	Urea	0.61	**<0.01****
	Createnine	0.57	**<0.01****
	T. Cholesterol	0.33	**0.02***

** (Significant p<0.01)

Grades of correlation (r): 0.00-0.24 (week association), 0.25-0.49 (fair), 0.50-0.74 (moderate), ≥ 0.75 (strong).

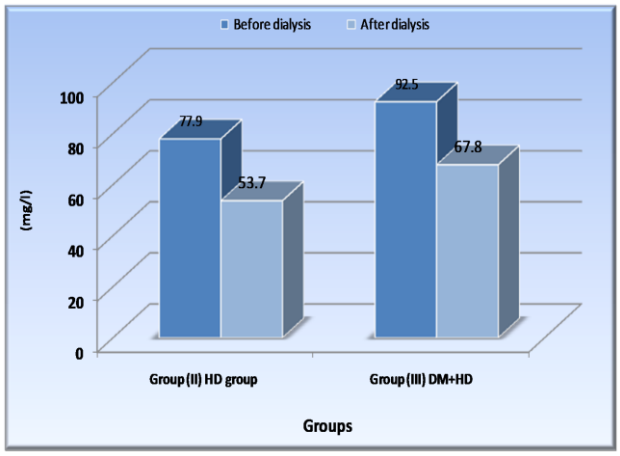

Figure (1): Fetuin-A level between group II and III before and after dialysis.

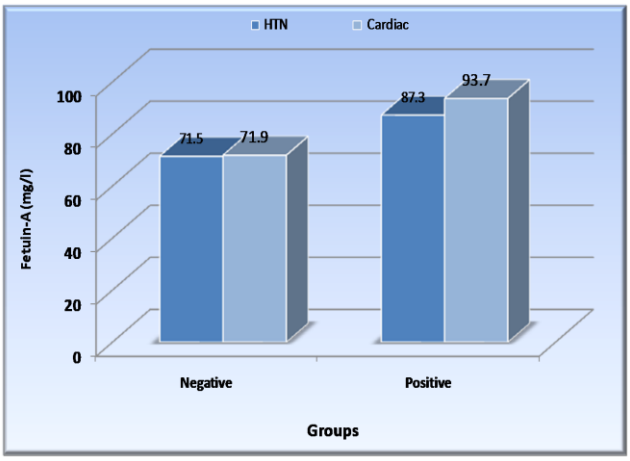

Figure (2): Comparison between Fetuin-A level in HTN and Cardiac negative and positive cases.

Discussion

Globally, diabetes mellitus is a major public health issue affecting millions of people and there are many complications associated with it DM such as nephropathy, neuropathy, cardiovascular and renal complications, retinopathy and food related disorders [(1)]. Diabetic nephropathy and its early prediction will help to prevent its hazards effectively. This study aimed to explore the effect and assesses the role of fetuin-A in diabetic and nondiabetic patients on hemodialysis. In this study, the three studied groups were almost comparable regarding baseline and demographic data. This non-significant difference is important to ensure the homogenization of the studied groups to get accurate results from the comparison between groups.

The main finding of this study demonstrated that there were significant differences among the three studied groups in Fetuin-A (the highest level was in DM+HD group followed by HD group however the lowest level was noticed in the control group, p< 0.01). Also, patients group (group II and group III) had significantly higher Fetuin-A level compared to the control group (p< 0.01). In addition, there

were significant differences between the two groups in Fetuin-A before dialysis and the same trend of results was found after dialysis. Also, Fetuin-A level was significantly decreased after dialysis compared to pre-dialysis values in group II and III ($p< 0.01$). Also, the significantly higher Fetuin-A levels were associated with HTN and cardiac affected cases. Furthermore, as expected, there were a highly significant positive correlation between Fetuin-A level and age, SBP, RBS, HbA1C, urea, createnine and T. cholesterol (all $p<0.01$). Similar results were found by Mohameda et al., [11] who found a significant difference in serum fetuin-A level in chronic renal failure (CRF) and diabetes patients. Also, they found a significant positive correlation between fetuin-A level and hemoglobin, serum Ca and albumin and finally they concluded that fetuin-A had a unique role as a biomarker of CRF in type 2 diabetes mellitus. Similarly, a recent Egyptian study reported that there was a highly significant increase in the fetuin-A levels in the diabetic patients with diabetic nephropathy compared to healthy control group [12]. Some studies reported that elevated circulating fetuin-A levels is strongly associated with and early-stage chronic kidney disease [5,6].

In line with or findings, increased fetuin-A in pre-diabetic patients is associated with increased progression to diabetes and decreased reversal to normoglycemia and is also used as a predictor of adverse glycemic outcomes in prediabetes [13]. Also, a previous study by Mehrotra et al., [14] reported that levels of fetuin-A were significantly higher among patients with diabetic nephropathy and they added that during predialysis stage of DN, there is a direct relationship between serum fetuin- A levels and CAC score. It has been reported that serum fetuin-A concentration was associated with mortality in dialysis patients [15]. Furthermore, a recent study by Perez-Sotelo et al., [16] found that Fetuin-A can be considered as a biomarker of nutritional status, and malnutrition in CKD patients. El-Batch et al., [17] found a significant increase in serum fetuin-A levels in microalbuminuric patients compared to normoalbuminuric patients and to control group. These results may be explained by the role of fetuin-A in mediating insulin resistance, lipid profile abnormalities and endothelial dysfunction which underlie the association between fetuin-A and abnormal albuminuria [17].

In a recent study, Mitkees et al., [18] found that the serum fetuin A is higher in patients with type 2 diabetes mellitus without micro-albuminuria compared to those with microalbuminuria. Also there was negative significant correlation between serum fetuin-A and albumin/ creatinine ratio in both groups; this means that high serum fetuin-A level could be used as early diagnostic marker before development of microalbuminuria in diabetic nephropathy. Fetuin-A induce apoptotic signals in the beta islets cells of the pancreas, reducing the secretion of insulin and further exacerbating T2DM [4]. Similar to our findings, Roshanzamir et al., [19], Mitkees et al., [18], Jamaati et al., [20], Sujana et al., [21] reported that increased Fetuin-A level was related with high level of SBP, HbA1C, urea, createnine and cardiac illness. Finally, this study has some limitations. Of these, the relatively small sample size and we could not include different biomarkers and compare among them. So, further studies with larger sample sizes and different settings are recommended to confirm our findings.

Conclusions

Fetuin-A was significantly higher in diabetic patients on hemodialysis compared to non-diabetic patients on hemodialysis and the normal healthy subjects. The role of serum fetuin-A may be far more complex than previously described. Elevated circulating concentrations of Fetuin-A may be a risk factor for conditions such as type 2 diabetes mellitus and impairment of kidney function. Further studies.

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