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Serum level of fetuin-A as a biomarker for vascular complications and severity of insulin resistance in individuals with type 2 diabetes

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Abstract
Background: Fetuin-A is one of the hepatokines that are capable of preventing vascular calcification. Furthermore, it induces metabolic dysfunction, IR and accompanied by elevated risk of DM. However, It remains a mystery whether fetuin-A is accompanied by risk of vascular complications in diabetics or not.
Aim of the work: To assess the association of serum fetuin-A, severity of IR and vascular complications in T2DM cases.
Patients and methods: In this cross sectional study we tested 160 T2DM cases; 80 patients with at least one of vascular complications and 80 patients without any vascular complications recruited from Endocrinology and metabolism unit, Internal Medicine Department, Tanta University Hospitals. Patients were assessed for DM vascular complications (Nephropathy, retinopathy, peripheral neuropathy and peripheral arterial disease).Serum fetuin-A level was assessed by ELISA, and the IR was evaluated via HOMA-IR.
Results: Lower fetuin-A level was accompanied by increased risk of vascular complications among T2DM cases and serum Fetuin-A had significant sensitivity 97.68% as a diagnostic marker to vascular complications among T2DM cases especially diabetic nephropathy (P=0.0001) with cut off value of 556.40 with +ve predictive values of 91.66% and -ve predictive values of 64.46%. Also low serum fetuin a level can be considered as a significant predictor and risk factor for vascular complications among type 2 diabetic patients. Increased serum fetuin-A level is accompanied by severity of IR as evaluated by HOMA-IR and it positively correlated with HOMAIR but without clinical significance
Conclusion: Lower serum fetuin a level is useful as a diagnostic biomarker and a significant predictor and risk factor for vascular complications among T2DM cases.

Keywords: Fetuin A, insulin resistance, vascular complications, biomarker, vascular calcification, type 2 DM

Introduction
Diabetes mellitus is considered a collective term that describes many heterogeneous metabolic disorders with the principal finding is chronic hyperglycemia. The etiology of DM is either a disturbance in the insulin production or various degrees of IR or often both [1]. In fact, great efforts are carried out to determine factors incorporated in the etiopathology of vascular complications in type II DM. despite the causes for advanced vascular diseases in type II DM aren't completely detected, IR or adipocytokines might participate in the etiopathogenesis of DM micro-& macro-angiopathies via modulation of the vascular function [2].
Fetuin-A is one of the multifunctional plasma factors produced predominantly by hepatocyte cells. Fetuin-A was proved to prevent ectopic Ca+2 deposition and guard against vascular calcifications in addition, Fetuin A was proved to have a physiologic inhibiting effect of insulin receptor tyrosine kinase and consequently is accompanied by IR, metabolic syndrome (MetS) in addition to high risk for T2DM [3]. In the fatty tissues, Fet-A causes down regulation of the expression of adiponectins, thus suppress the anti-inflammatory as well as insulin-sensitizing effects of them [4]. Fetuin-A was proved to have pro as well as anti-inflammatory effects. Fetuin A has bidirectional action. On one hand, fetuin-A can acts as one of the endogenous ligands for TLR4 that cause activation TLR4-signaling via FFA to

promote IR, and induce the formation of pro- inflammatory cytokines from adipocyte and macrophage cells. On the other hand, fetuin-A has a crucial role in inhibiting the pro-inflammatory cytokines, TNF, TGF-β1 antagonization and regulation of macrophage polarization [5].

Epidemiologic studies suggested that serum fetuin-A has an association with IR and its comorbidities, such as MetS [6] and type II diabetes [7]. Other studies linked excesse plasma fetuin-A to the elevated risk of MI and ischaemic stroke [8]. whereas, decreased fetuin-A range is accompanied by mortality and CVD problems in patients suffering ESRD [9]. However, conflicting results were documented as regard the importance of new biomarker fetuin-A in macroangiopathy in cases suffering type II diabetes. Furthermore, there's scarce data concerning the association of fetuin-A with microangiopathy in type II diabetes. Therefore, the current study aimed at investigating the association between serum fetuin-A and insulin resistance and vascular complications in cases with type II diabetes.

Patients and Methods

This cross sectional study was carried out on 160 type 2 DM cases: 80 with at least one vascular complication and 80 without vascular complication. The patients were recruited from Endocrinology and metabolism unit, Internal Medicine Department, Tanta University Hospitals during the period from May 2021 to May 2022.

This study agreed with the ethical guidelines of the Declaration of Helsinki and followed the ethical standard of Tanta Faculty of Medicine. We asked all cases for informed consents according to the local ethical committee. Privacy of the data of all cases patients was granted and we gave a code number for every case file that included all investigations.

Cases with Type 1 DM, Chronic liver disorders other than NAFLD, Chronic inflammatory and infectious diseases, Diabetic patients taking Ca+2 or Vit D supplementations and Diabetic patients receiving insulin-sensitizers were excluded from our study. Blood sample was collected after overnight fasting in a tube contain a clot activator and left to clot for 30 minutes before centrifugation for 20 min at 3000rPm, after centrifugation one part of the serum sample was stored at -20 °C for assay of Fetuin A, insulin and the other part was immediate used for routine lab investigation that included FBG, Cholesterol, TGs, LDL, HDL, Blood urea and serum creatinine. While 2 h post prandial blood sample withdrawn 2 hours after the meal.

All cases were subjected to: complete history taking

Complete clinical assessment: Focusing on waist circumference, Wt, and height, BMI was calculated as weight (Kg) / [height (in)]2 fundus examination to assess diabetic retinopathy, it was categorized as normal, NPDR and PDR. The patient was considered to have DR if HE/SHE showed NPDR and PDR stage.

Diabetic peripheral neuropathy diagnosis in cases showing the following criteria: typical subjective neuropathic manifestations that included symmetrical distal neuropathy, insensitivity to a 10 g monofilaments, altered pinprick sensations and vibration sense on doing the test with a 128-Hz tuning fork.

Peripheral arterial disease [10] was diagnosed clinically by prescence of the following signs in the leg: coldness in leg or foot, leg weakness(muscle atrophy),skin color changes, smoot and shiny skin with hair loss, decreased or absent pulse in the feet and presence of sores or ulcers in the legs or feet that don't heal.

Also Ankle brachial index was done for diagnosis of PAD: (ABI) measured as the SB at the ankle, divided by the SB at the arm. It was confirmed to be a specific as well as sensitive metric for diagnosing PAD.

- Normal ABI ranged between 0.9 and 1.4.
- Values above 1.4 suggest a non-compressible calcified vessels.
- Values 0.8 - <0.9 is suggests mild PAD.
- Value 0.5 -<0.8 is suggests moderate PAD.
- Values less than 0.5 suggests severe PAD.

DN was detected via detection of albuminuria that was assessed by radioimmunoassay. Urinary albumin less than 30 mg/gm Cr was considered normoalbuminuric, urinary albumin of 30–300 mg/gm Cr was considered as microalbuminuria and urinary albumin of 300 mg/gm Cr was considered as overt proteinuria. The patient was categorized to have nephropathy if he/she had microalbuminuria or overt proteinuria. eGFR was calculated via CKD-EPI (CKD Epidemiology Collaboration) equation [11].

Laboratory investigations including

Fasting, postprandial blood glucose,HBA1C,Lipid profile that included (Cholesterol, triglyceride, LDL-c and HDL-c), Blood urea, serum creatinine, Alb/creatinine ratio was measured using radioimmunoassay, plasma levels of Fetuin-A was estimated via ELISA technique and Fasting Serum levels of insulin was estimated by ELISA technique.

- HOMA-IR values were measured based on HOMA model formula: HOMA-IR=fasting insulin (mlU/l)×fasting glucose (mg/dl)/405. We considered HOMA-IR: less than 2 normal, 2-2.9:early IR and more than 2.9 significant IR.

Statistical Analysis

The results were coded, entered, tabulated to be statistically analyzed via SPSS version 23 (IBM Corporation, Armonk, NY, USA) [12].

For quantitative results, the range, mean, median and SD were calculated. Boxplots were carried out to explain lower & upper limits, median, 1st and 3rd quartiles of the quantitative data. For qualitative data that describes a categorical group of results by frequency, % or proportion of each category, comparing between 2 groups was carried out via Chi-square test (χ^2); while student t-test to compare between means of 2 groups of parametric data of independent variables. Z value of Mann-whitney test for Comparing between means 2 groups of non-parametric results of the independent sample, for comparison between ≥2 means of non-parametric data, Kruskal-Wallis (χ^2) values were estimated. Correlation between variables was evaluated using Pearson's correlation coefficient (r). The ROC curve was performed for detection of the AUC that denotes the sensitivity and specificity of serum Fetuin-A and other biomarkers in diagnosis of vascular complications among T2DM cases. The cutoff value of Fetuin-A biomarker was calculated from the ROC curve

To detect the existence of vascular complications according to a group of predictor variables or independent variables (Serum Fetuin-A and some other biomarkers) among type II DM cases, multivariate binary logistic regression was done.

Logistic regression coefficient (B) was utilized for estimation of Odds ratios (EXP (B)) of them as risk factors and predictors for vascular complications.

Results: Our study included 160 T2DM cases. The cases were subdivided into 2 groups Group (I): 80 type 2 diabetic patients with at least one vascular complications, Group (II): 80 T2DM cases without any vascular complications. Frequency of complications among the studied T2DM cases with vascular complications are shown in table (1).

Table 1: Frequency of complications among the studied type 2 diabetics with vascular complications

Variables	The studied T2DM cases with vascular complications (n=80)	
	n	%
Neuropathy		
No	12	15.0
Yes	68	85.0
Fundus vascularity		
Normal	25	31.3
Non proliferative	31	38.8
Proliferative	24	30.0
Nephropathy (Proteinuria)		
No	8	10.0
Yes	72	90.0
Albuminuria (Albumin/Creatinine ratio)		
Normal	8	10.0
Microalbuminuria	61	76.3
Macroalbuminuria	11	13.8
Severity of arterial disease		
Normal (0.9-1.4)	68	85.0
Mild arterial disease (0.8 - <0.9)	5	6.3
Moderate arterial disease (0.5 -<0.8)	7	8.8
Severe arterial disease(<0.5)	0	0

Our study showed statistically Higher HBA1c, serum urea, Cr and A /Cr ratio in diabetic group with complication, Also there was statistically lower fasting blood insulin and EGFR in complicated group whereas no significant differences were proved between the studied groups as regard BMI, Waist circumference, FBG, post prandial blood glucose, HOMAIR, Lipid profile and Ankle brachial index, as shown in table (2).

Table 2: Demographic, clinical and laboratory data of the TWO groups

Variables	The studied type 2 diabetic patients (n=160)		t	p
	Group 1 (n=80)	Group 2 (n=80)		
Age years	56.05±9.61	53.00±8.61	2.213	0.036*
Sex [n (%)]				
Female	53 (66.3)	57 (71.3)		**0**.465
Male	27(33.8)	23(28.7)		0.495
Body mass index (BMI)	30.14±3.13	30.17±2.96	0.054	0.957
waist circumference(cm)	103.65±9.97	104.31±9.57	0.428	0.669
Fasting blood glucose (mg/dl)	265.57±70.22	248.79±64.49	1.575	0.117
Post-prandial blood glucose (mg/dl)	313.51±77.29	301.84±64.07	1.040	0.300
Fasting blood insulin (FBI) (MIU/ml)	8.14±3.57	10.05±4.48	2.979	0.003*
HOMA-IR	5.11±2.34	5.93±2.89	1.976	0.050
Glycated HB (HBA1c)	9.38±0.91	7.76±0.79	12.037	0.0001*
Blood urea (mg/dl)	33.35±23.60	23.32±8.13	3.592	0.0001*
Serum creatinine (mg/dl)	0.98±0.48	0.77±0.15	3.651	0.0001*
Albumin/Creatinine ratio	188.41±213.88	10.51±5.85	10.438	0.0001*
EGFR	83.56±26.58	94.64±15.72	3.207	0.002*
LDL (mg/dl)	104.39±25.51	98.87±27.50	1.317	0.190
HDL (mg/dl)	50.40±11.94	52.34±13.98	0.944	0.347
Total cholesterol (mg/dl)	189.10±48.36	186.71±63.31	0.268	0.789
Triglycerides (mg/dl)	126.62±55.23	135.34±95.83	0.705	0.482
Ankle-brachial index	1.07±0.15	1.10±0.08	1.639	0.103
Serum Fetuin-A (mg/l)	627.43±262.16	1197.84±504.58	9.279	0.0001*

*Significant <0.05

Regarding Fetuin A in both groups, Fetuin A showed significant decrease in diabetic group with complication (p=0.0001) as in Table (2) and Figure (1).

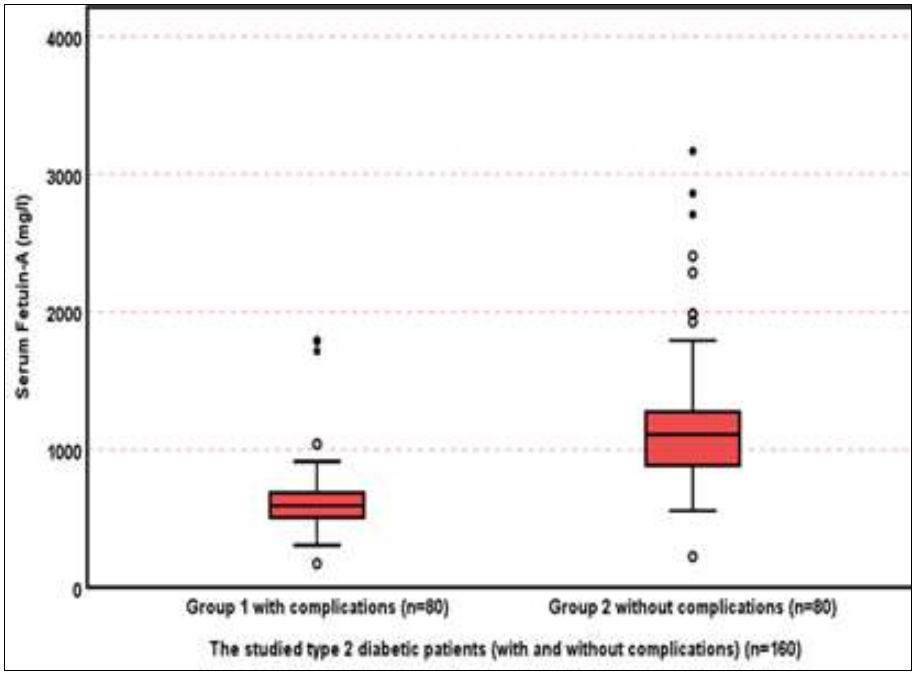

Fig 1: Boxplots of serum Fetuin-A of the studied T2DM (with & without vascular complications)

Regarding the relation between fetuin A level and each vascular complication, our results showed relatively lower fetuin A level in group with neuropthy compared to the other group (Table 3), Also Fetuin A was relatively lower in cases with prolifertive retinopathy than cases with non-proliferative changes and cases without retinopathy (table 4), And Also relatively lower fetuin A level in cases having moderate PAD than patients with mild PAD and patients without PAD(table 5)with no significant differences between the studied groups concerning neuropathy, retinopathy and PAD.

Our results showed significant lower Fetuin A levels in diabetic cases with nephropathy in comparison with cases without nephropathy (p=0.003*). And significantly lower fetuin A in cases with macroalbuminuria in comparison with cases with microalbuminuria and cases without albuminuria (p=0.0001*) as showed in figure (2, 3).

Table 3: Serum Fetuin-A of the studied T2DM (with and without neuropathy).

Serum Fetuin-A	The studied type 2 diabetic patients (n=80)		Z value	P value
	With neuropathy (n=68)	Without neuropathy (n=12)		
Serum Fetuin-A				
Range	379.70-755.80	172.30-1794.00	0.990	0.332
Mean±SD	562.17±103.25	638.94±279.98		

Table 4: Serum Fetuin-A of the studied type 2 diabetic patients in relation to fundal vascular changes

Serum Fetuin-A	Fundal vascularity of the studied type 2 diabetic patients (n=80)		
	Normal fundus (n=25)	Non proliferative (n=31)	Proliferative (n=24)
Serum Fetuin-A			
Range	305.30-1784.00	341.50-1794.00	172.30-913.80
Mean±SD	673.51±320.08	616.68±269.09	579.09±146.46
χ^2 value	1.163		
P value	0.559		

Table 5: Serum Fetuin-A in relation to severity of arterial disease (ABI) of the studied T2DM cases with vascular complications

Serum Fetuin-A	Severity of arterial disease (ABI) of the studied type 2 diabetic patients (n=80)		
	Normal (n=68)	Mild arterial disease (n=5)	Moderate arterial disease (n=7)
Serum Fetuin-A			
Range	305.30-1794	448.80-587.90	172.30-694.30
Mean±SD	648.79±274.31	526.12±54.19	492.26±166.38
χ^2 value	4.943		
P value	0.084		

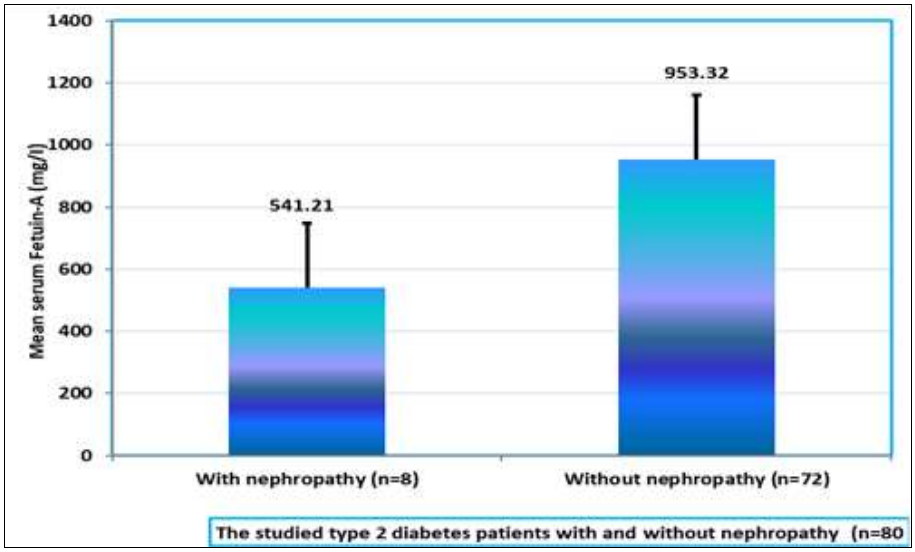

Fig 2: Mean values of plasma Fetuin-A of the studied T2DM cases (with and without nephropathy)

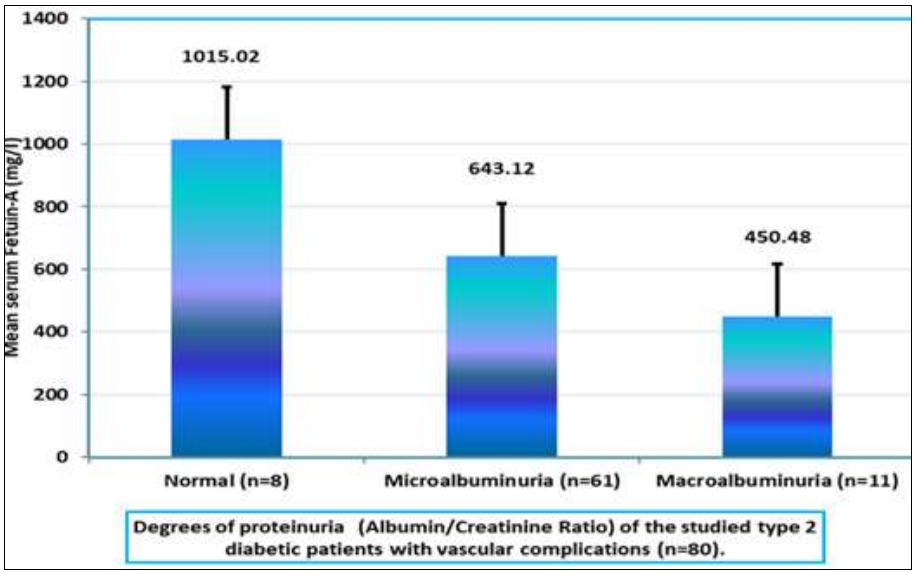

Fig 3: Serum Fetuin-A in relation to (Albumin/Creatinine ratio) of the studied type 2 diabetic patients with vascular complications

Our Results showed also relatively higher mean values of Fetuin A in patients with significant insulin resistance than patients with normal and early insulin resistance with no statistically significant difference regarding severity of IR in both diabetic groups. Also there was non- significant correlation between fetuin A level and HOMA IR in both diabetic groups As showed in table (6).

Table 6: Serum Fetuin-A in relation to severity of IR of the studied T2DM cases (With and without vascular complications).

Severity of insulin resistance	Serum Fetuin-A of the studied type 2 diabetic patients (n=160)	
	Group 1 (n=80)	Group 2 (n=80)
	Range Mean ±SD	Range Mean ±SD
Severity of insulin resistance		
-Normal	-	1196.14
-Early insulin resistance	341.50-805.30 553.67±18.91	222.87-3166.50 1298.30±514.71
-Significant insulin resistance	172.30-1794 640.44±278.51	878.60-3166.50 1780.35±1565.81
Z value or χ^2 value	1.186	1.246
P value	0.236	0.313
r	0.296	0.161
P	0.399	0.592
(Correlation of Fetuin-A & HOMA-IR)		

The receiver operating characteristic curve (ROC) curve revealed that FetuinA has significant sensitivity 97.68% as a diagnostic marker to vascular complications among type 2 diabetic patients(P=0.0001) with cut off value of 556.40,with +ve predictive values of 91.66% and -ve predictive values of 64.46% (table 7) (fig 4,5).

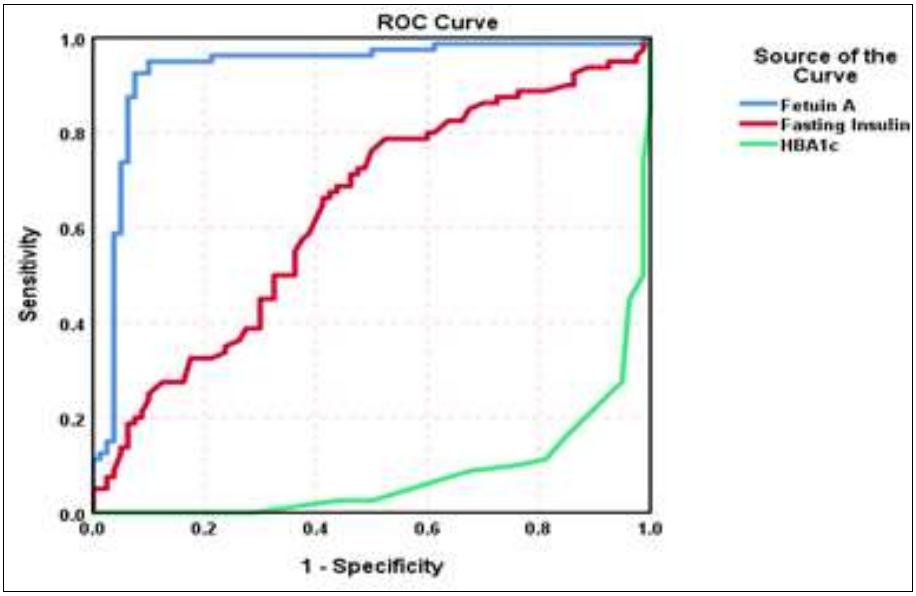

Fig 4: Area under ROC curve denoting sensitivity & specificity of serum fetuin-A as diagnostic biomarker in comparison to glycemic biomarkers for vascular complications among type 2 diabetic patients

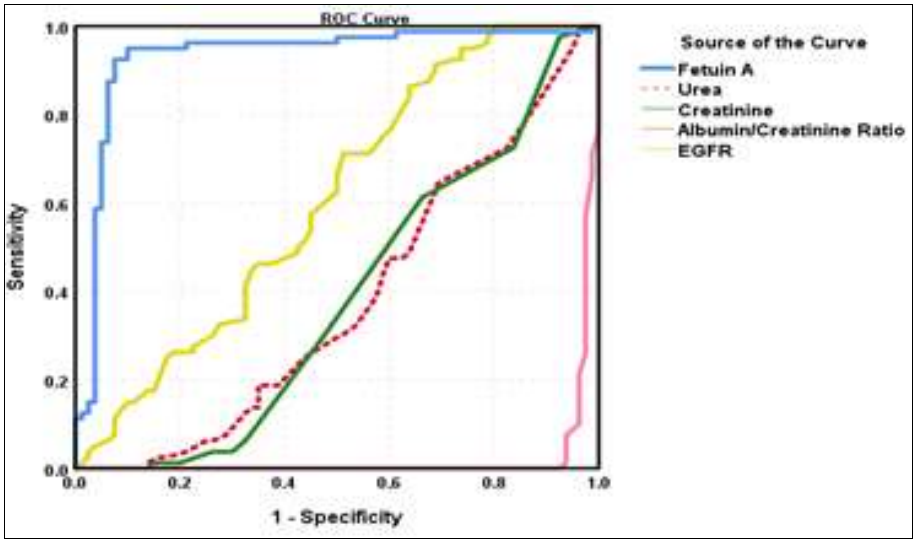

Fig 5: Area under ROC curve denoting sensitivity & specificity of serum fetuin-A as diagnostic biomarker in comparison to renal function parameters for vascular complications among type 2 diabetic patients

Table 7: Sensitivity, specificity, PPV&NPV of serum Fetuin-A as diagnostic biomarker among the studied type-2 diabetes

Serum Fetuin A as diagnostic biomarker	Sensitivity	Specificity	+ve predictive values	-ve predictive values
Diagnostic to vascular complications among type 2 diabetic patients	97.68%	72.5%	91.66%	64.46%

Binary logistic regression analysis (Table 8) showed that Serum Fetuin-A and glycated hemoglobin (HBA1c) are highly significant predictors to vascular complications T2DM cases (P=0.0001 and 0.0001 respectively). Also, HOMA-IR followed by Albumin/creatinine ratio, were significant risk factors and predictors to vascular complications in T2DM cases (P=0.006 and 0.003 respectively).

Table 8: Binary logistic regression analysis (Multivariate) of serum fetuin-A biomarker in comparison to other biomarkers as predictors for vascular complications among type 2 diabetic patients

Variables	B	SE	Sig. (P value)	EX (B)	Confidence interval (CI)	
					Lower limit	Upper limit
Serum Fetuin-A (mg/l)	0.004	0.001	0.0001*	1.004	1.002	1.006
HOMA-IR	1.224	0.449	0.006*	3.401	1.412	8.192
HBA1c	5.089	1.175	0.0001*	0.006	0.001	0.062
Albumin/Creatinine Ratio	0.234	0.078	0.003*	0.791	0.679	0.922
EGFR	0.007	0.056	0.904	1.007	0.902	1.124
Ankle-brachial index (ABI)	1.533	1.666	0.166	0.201	0.014	3.554

Discussion

DM is considered a crucial health problem globally. Over the last years, the prevalence of type II DM becomes an epidemic proportion due to the increase in the prevalence of obese individuals as well as the unhealthy lifestyles all over the world [13].

In fact, great efforts are carried out to determine factors incorporated in the etiopathology of vascular complications in T2DM. Thus, we aimed in this research to detect the correlation between plasma fetuin-A, severity of IR and vascular complications in T2DM cases.

In our study Fetuin A was markedly decreased in diabetics group with complication than group without complication (p=0.0001) and this result is in agreement with Birukov A, *et al.* 2022 [14] they found that decreased pre-diagnosis fetuin-A level was accompanied by increased risk of vascular complications. The probable mechanisms for the protective effects of fetuin-A to prevent DM-related vascular complications progression might be because of its efficient inhibitory effect on the pathological vascular mineralization process [14]. Also our data are congruent with Eraso *et al.* 2010 [15] and Roos *et al.* 2010 [16] they found that fetuin-A was inversely associated with PAD in diabetic patients. Also Emoto *et al.* 2010 [17] found inverse associations between fetuin-A and the prevalence of atherosclerotic calcified plaques.

Contradictory to our result. Yin L *et al.* 2015 [18] postulated that high serum fetuin-A level was accompanied by macroangiopathy in cases with recent-onset type II DM. Also Ou *et al.* 2015 [19] found that Fetuin-A is accompanied by subclinical CVD and accidental or fatal CVD as it causes more aggravation in the arteries stiffness in DM and by its correlation with Met S and atherogenic lipids. And also Al-Said NH *et al.* 2018 [20] found that elevated Fetuin A level is accompanied by diabetic microvascular complication especially diabetic nephroparhy. Also Jung *et al.* 2013 [21] study exhibited that high plasma fetuin-A is significantly accompanied by arteries stiffness yet no correlation with any microangiopathy in cases suffering type II DM.

In our study patients with neuropathy have non-significant lower mean values of fetuin A than patients without neuropathy, and this result is the same as Birukov A *et al.* 2022 [14] they concluded that lower fetuin A level was accompanied by increased incidence of neuropathy in diabetics. In contrast to the current result Roos *et al.* 2010 [16] and Jung *et al.* 2013 [21] found no correlation between fetuin A level and DN as well as Cardiac autonomic neuropathy.

In our study serum Fetuin A levels were relatively lower in PDR than NPDR and diabetics without retinopathy without statistical significance between groups and such results are the same as Birukov A *et al.* 2022 [14] as they found that lower fetuin A level is accompanied by increases risk of diabetic retinopathy. In disagreement with our result, Zhao *et al.* 2015 [22] and Yilmaz *et al.* 2018 [23] found that Fetuin-A value of diabetics increased based on the stage of DR. While In a study by Mostafa *et al.* 2022 [24] Fetuin-A was proved to have non-significant roles in the etiopathogenesis of DR.

As regard diabetic nephropathy, our study showed that patients with nephropathy have significant decrease in the mean value of fetuin A than cases without nephropathy, Also there were significant lower mean values of fetuin A in patient with macroalbuminuria in comparison with cases with micro and normo-albuminura (p=0.003)(p= 0.0001)respectively. such result is similar to Birukov *et al.* 2022 [14], they found that lower values of fetuin A is accompanied by high risk of DN. Also A Mitkees *et al.* 2020 [25] revealed that Serum Fetuin A is increased in diabetics without microalbuminuria than those with microabuminria and there were Significant negative correlations between serum Fetuin A and A/C ratio in diabetics with and without microalbuminuria., Also Umapathy *et al.* 2022 [26] found that An important stepwise reduction was determined in the circulatory Fetuin-A in cases with persistent macroalbuminuria compared to micro and normoalbuminuria.

In disagreement with our result Al-Said *et al.* 2018 [20] revealed a markedly significant increased fetuin A level in the diabetics suffering nephropathy than patients without nephropathy, Also, El-Batch *et al.* (2015) [27] found a significant elevation in serum fetuin A level in diabetic microalbuminuric cases in comparison with normoalbuminuric cases and this result was explained by the effect of fetuin-A in mediation IR, lipid profile abnormality and dysfunction of the endothelium.

As regard ABI and severity of arterial disease: fetuin A has lower mean values in cases having with moderate arterial disease in comparison patients with mild and without PAD with no statistically significant differences between the groups, this result in agreement with Eraso *et al.* 2010 [15], Eleftheriadou *et al.* 2017 [28], Abd El-Fattah *et al.* 2017 [29], all these studies revealed that decreased fetuin A level was accompanied by PAD in T2DM and they explained their results by its inhibitory effect on vascular calcification.

In disagreement with our result Lorant *et al.* 2011 [30], Jung *et al.* 2013 [21], Morsy *et al.* 2020 [31], all these studies concluded that elevated fetuin A was accompanied by PAD and HIGH risk of atherosclerosis in T2DM with negative correlation with ABI by its association with MS and atherogenic lipids.

As regard Fetuin A and severity of IR, In our study, Fetuin A shows higher mean values in patients with significant insulin resistance than patients with normal and early insulin resistance in the two groups without statistically significant differences between them. Also non-significant correlations were proved between HOMA-IR and level of serum Fetuin-A. This result is in agreement with Jung *et al.* 2013 [21], Yin *et al.* 2014 [32], El-Messallamy *et al.* 2020 [33]. These research found that higher fetuin A is accompanied by insulin resistance and there was a positive correlation between insulin resistance and HOMA IR. As fetuin-A can prevent phosphorylation of hepatic and muscular insulin receptors, this results in a decreased insulin signaling causing IR in T2DM. Fetuin-A can promote IR via inhibiting the insulin receptor tyrosine kinase through induction FFA inflammatory signaling by toll like receptors promoting FA accumulation, FFA mediated inflammation of pancreatic β-cells contributes to IR [33].

In disagreement with this result Mori *et al.* 2006 [34] found that serum fetuin-A level showed significant correlation with insulin resistance (HOMA IR) in non-diabetics subjects, in contrast, they found no association of fetuin-A with IR in T2DM cases, this result was explained by that Under diabetic conditions, stronger determinants like glucose toxicity in addition to/or protein modification like non-enzymatic glycation may overcome and veil the influence of fetuin-A on IR.

There are many limitations of the current we can address; 1st, since its a cross-sectional study, we couldn't detect the causative relationship among fetuin-A, IR and DM complications so Prospective studies will be necessary to explain such pivotal important question. 2nd, the small number of patients were included. So, large numbers of cases require assessment to confirm our results. Third, HOMA-IR was utilized as an index of IR that might not give precise results in cases having markedly impaired or even lacking β-cell functions and in diabetics under insulin therapy or insulin secretagogues, so further studies assessing HOMA IR with fetuin a level in obese non-diabetics and prediabetics is required. Fourth, no direct measurement of vascular calcifcation was available, a false-negative ABI results might happen in cases suffering non-compressible arteries. Heavy calcification of the lower-extremity vessels might artificially increase the ankle pressure measurements, so further studies assessing the relation of vascular calcifications of vessels and serum fetuin a level is required.

Conclusion

Lower fetuin-A levels was accompanied by increased risk of micro and macro vascular complications among type 2 diabetic patients and serum Fetuin-A had significant sensitivity 97.68% as a diagnostic marker to vascular complications among T2DM cases especially diabetic nephropathy (P=0.0001) with cut off value of 556.40, with +ve predictive values of 91.66% and -ve predictive values of 64.46%. Also reduced serum fetuin A level can be considered as a significant predictor and risk factor for vascular complications among type 2 diabetic patients elevated serum fetuin-A level was accompanied by severity of IR as evaluated via HOMA-IR and it positively correlated with HOMAIR but without statistical significance.

Conflicts of interest

Not available.

Funding

Not available.

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