

# Fetuin-A and YKL-40 serum levels and carotid intima-media thickness: Could they be good predictors for mild to moderate erectile dysfunction?

## Original Article

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## ABSTRACT

**Background:** Erectile dysfunction (ED) has been reported to occur as an early manifestation of atherosclerosis. Fetuin-A and YKL-40, (N-terminal amino acid: tyrosine (Y), lysine (K), leucine (L) and its molecular mass 40 kDs) which are glycoproteins secreted by many cells, significantly participate in formation of vascular tissue in healthy and diseased states.

**Objective:** This study aimed at assessment of serum fetuin-A and YKL-40 levels and the carotid intima-media thickness (CIMT) in patients with mild-moderate as well as moderate ED in comparison with control group.

**Patients and Methods:** A total of 90 patients with ED (grade mild-moderate) and 30 healthy participants who attend the outpatient clinic of the Andrology Department, Alexandria Main University Hospital, were included in the study. Enzyme-linked immunosorbent assay was used for measuring both serum fetuin-A and serum YKL-40, and high-resolution B-mode ultrasound was used to measure the CIMT.

**Results:** Statistically significant low fetuin-A and high YKL-40 serum levels as well as a significant increase in CIMT were detected in patients with ED compared with controls. In addition, the ED severity showed a negative and positive correlation to fetuin-A and YKL-40 serum levels, respectively, but there was no correlation to CIMT.

**Conclusion:** fetuin-A and YKL-40 may be used as a predictor for cardiovascular risks in patients with mild to moderate ED..

**Key Words:** Carotid intima-media thickness, erectile dysfunction, fetuin-A, YKL-40.

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## INTRODUCTION

Erectile dysfunction (ED) is a frequently encountered disorder of male sexual function, manifested, at any age, as a failure to achieve and/or maintain an erection sufficient for a satisfactory sexual intercourse, which significantly negatively affects the patient's quality of life<sup>[1,2]</sup>.

Endothelial dysfunction has been detected in both cardiovascular diseases and ED. It is characterized by a reduced production of nitric oxide (NO) which stimulates vasodilation and enhances the vascular permeability to some plasma proteins, like the low-density lipoproteins (LDL), as well. This defect leads to vasoconstriction, platelet aggregation, and leukocyte adhesion<sup>[3]</sup>.

Fetuin-A is a glycoprotein that inhibits the process of calcification. The decrease and increase in its serum level may contribute to the process of inflammation and then atherosclerosis<sup>[4]</sup>.

YKL-40, a 40-kD chitin-binding glycoprotein, is an acute-phase protein produced in many cells, such as macrophage. It modulates tissue remodeling as well as acute and chronic inflammatory processes<sup>[5-7]</sup>.

It was previously documented that YKL-40 has a pathogenic role in early atherosclerotic process, leading to endothelial dysfunction and progression of the disease, which leads to cardiovascular clinical manifestations<sup>[5,6]</sup>. Serum YKL-40 has been found to be abnormally high in cardiovascular diseases like peripheral artery disease<sup>[8]</sup>, coronary artery disease<sup>[9]</sup> and stroke<sup>[10]</sup>.

Carotid intima-media thickness (CIMT) is frequently used in epidemiological and interventional studies as an important marker for early or subclinical atherosclerosis. Yet, data on the relationships between inflammatory biomarkers such as fetuin-A and YKL-40 and CIMT in patients with ED are insufficient<sup>[11]</sup>.

This study evaluated the serum YKL-40 and fetuin levels and CIMT in patients with ED (grade mild-moderate)

to detect their relationship with the severity of the disease.

## PATIENTS AND METHODS

A total of 90 male patients (group A) with either moderate or mild to moderate ED were recruited from outpatient clinic of Venereology and Andrology Department, Alexandria Main University Hospital, and 30 age-matched healthy hospital staff members serving as controls (group B). All participants signed an informed written consent before joining the study.

Approval of the Ethics Committee of the University of Alexandria was obtained and the study committed to the ethical principles of the Declaration of Helsinki.

Patients with clinical history of coronary artery disease, dyslipidemias, diabetes mellitus (fasting glucose levels >110 mg/dl), kidney dysfunction, or anatomical disorder of penis; patients with major psychiatric or neurogenic disorders and patients receiving medications that affect sex hormones or other medications for ED or dyslipidemias (6 months before the study) were excluded.

Participants were clinically examined mainly to assess the testicular size. The International Index of Erectile Function-5 (IIEF-5) questionnaire, a validated, self-administered, multidimensional tool, was used to define the severity of the ED<sup>[12]</sup>. Scores indicate the following: No ED if greater than or equal to 22, mild ED if 17–21, mild-moderate ED if 12–16, moderate ED if 8–11, and severe ED if 1–7 indicated. Patients were assigned to one of the two groups according to the severity of their ED [22 patients (mild-moderate) and 38 patients (moderate)].

### Laboratory investigations

Twelve-hour fasting blood samples were withdrawn between 8 a.m. and 10 a.m. to measure blood glucose, total cholesterol, LDL, high-density lipoprotein (HDL), and triglycerides using the autoanalyzer and applying the standard enzymatic methods (Cobas 311; Roche Diagnostics, Mannheim, Germany). Moreover, free testosterone was measured by the enzyme-linked immunosorbent assay method using a kit from Calbiotech (Austin, Texas, USA), whereas prolactin (PL) and total testosterone were measured by the chemiluminescent immunoassay (Architect Plus 1000 SR; Abbot Diagnostics, USA).

Serum samples were stored at  $-20^{\circ}\text{C}$  until time of the assay analysis. YKL-40 and fetuin-A concentrations in EDTA plasma were measured in duplicates using a commercial enzyme-linked immunosorbent assay (Quidel, Santa Clara, California, USA). The cat number of human YKL-40 was EK0974, and its minimum detectable dose was less than 1.22 mg/ml, whereas the cat number of fetuin-A was EK0757, and minimal detection limit was 0.04 ng/ml.

### Radiological investigation

#### Measurement of carotid artery intima-media thickness

CIMT is a low-level echo gray band which does not project into the arterial lumen, represented, in duplex ultrasound system with 7.5 MHz scanning frequency in the B-mode, pulsed Doppler mode, and color mode, as the distance between the leading edge of the first and second echogenic lines of the distant arterial walls during diastole<sup>[13]</sup>. CIMT was evaluated, while patient is in the supine position, in plaque-free arterial segments of both the right and left common carotid arteries (3 cm before the carotid bifurcation) and internal carotid artery (2 cm distally from the carotid bifurcation). The same radiologist performed all measurements to exclude bias.

A high-resolution ultrasound (Siemens, ACUSON X 300 PE Ultrasound System, Siemens Medical Solutions, USA, Inc., California, USA), equipped with an VF13-5 wide bandwidth linear transducer, was used. The average value of both carotid arteries CIMT was calculated<sup>[14,15]</sup>.

#### Statistical analysis of the data<sup>[16]</sup>

IBM SPSS software package version 20.0. (IBM Corp., Armonk, New York, USA) was used for data tabulation and analysis. Normal distribution of the quantitative data was determined by the Kolmogorov–Smirnov test. Quantitative data were expressed as a range (minimum and maximum), mean, SD, and median.  $\chi^2$  test was used to compare categorical variables and analyzed the significance between the different stages in different stages and groups. Quantitative data with a normal distribution were analyzed by the Student t-test. However, analysis of quantitative data with an abnormal distribution was done by the Mann–Whitney test as well as the Kruskal–Wallis test, and their associations were detected by the Spearman coefficient. Pairwise comparisons were done by the post-hoc (Dunn's multiple comparisons test), whereas comparison of data of more than two groups was done by the F-test (analysis of variance). Significance level was set at 5%.

## RESULTS

Demographic, clinical, and laboratory findings of all participants are depicted in Table 1. Insignificant differences were detected between both groups regarding age, marital status, smoking behavior, blood pressure, testicular size, fasting blood glucose, lipid profile (serum cholesterol, TG, LDL, and HDL), serum testosterone (total and free), and serum PL (Table 1).

Our results showed significantly lower fetuin-A and significantly higher serum YKL-40 in the studied group compared with controls ( $P < 0.001$ ) (Table 1). Moreover,

serum fetuin-A level was significantly negatively correlated with serum YKL-40 level ( $P=0.032$ ).

Patients with moderate ED had a significantly higher serum YKL-40 and a significantly lower mean serum fetuin-A compared with those with mild-moderate ED (Table 2).

Moreover, IIEF-5 score was significantly positively correlated with fetuin-A and significantly negatively correlated with YKL-40 ( $P<0.001$ ) (Fig. 1a and b).

The best cutoff value of serum fetuin-A and serum YKL-40 in the ROC curve in ED group was less than or equal to 1.911 and greater than 315.65ng/dl, respectively. The confidence interval of these predictive values was 0.621–0.890 ( $P=0.007$ ) in serum fetuin-A and 0.802–0.993 ( $P<0.001$ ) in serum YKL-40. The area under the curve of 0.751 in serum fetuin-A and 0.898 in serum YKL-40 (Fig. 2a).

Serum fetuin-A and serum YKL-40 could predict moderate ED at the cutoff point of less than or equal to 1.834ng/ml and of greater than 456.45ng/ml, respectively.

The area under the curve was 0.863 for serum fetuin-A and 0.972 for serum YKL-40. The confidence interval of serum fetuin-A was 0.729–0.729 ( $P<0.001$ ) and serum YKL-40 was 0.923–1.0 ( $P<0.001$ ) (Fig. 2b).

However, serum fetuin-A and YKL-40 could predict mild-moderate ED at a cutoff point of less than or equal to 1.79ng/ml and greater than 532.2ng/ml, respectively; the area under the curve was 0.823 in serum fetuin-A and 0.909 in serum YKL-40, and a confidence interval of 0.668–0.977 ( $P<0.001$ ) in serum fetuin-A and 0.747–0.983 ( $P<0.001$ ) in serum YKL-40 (Fig. 2c).

The intima-media thickness of both common carotid arteries as well as the average value was significantly higher in ED cases than controls ( $P<0.001$ ) (Table 1). Yet, there was no significance correlation with fetuin-A and YKL-40 serum levels. Similarly, the mean diameter of average common CIMT did not correlate with age of the patients, duration of the disease, atherogenic lipid profile, hormonal parameters, or with the IIEF-5 score ( $P=0.758$ ) (Fig. 3 and Table 3).

**Table 1:** Comparison between the two studied groups according to different parameters

	Cases (n=90) [n (%)]	Control (n=30) [n (%)]	Test of significance	P
Age (years)	45.6±3.2	45.7±2.9		0.99
Marital state				<sup>FE</sup> P=1.000
Unmarried	9 (10.0)	4 (13.3)		
Married	81 (90.0)	26 (86.7)		
Smoking				
Non-smoker	63 (70.0)	14 (46.7)		0.128
Smoker	27 (30.0)	16 (53.3)		
Testis size (mm)				
Right	15.0±2.85	15.53±2.75	t=0.598	0.553
Left	14.93±3.10	16.53±2.29	t=1.769	0.084
Average	14.97±2.91	16.03±1.88	t=1.288	0.204
FBG (mg/dl)	88.0±8.15	84.53±6.03	t=1.457	0.152
Lipid profile				
Serum cholesterol (mg/dl)	145.40±22.98	134.40±15.25	t=1.674	0.101
TG (mg/dl)	86.0±22.54	75.47±16.47	t=1.605	0.116
LDL (mg/dl)	85.27±10.86	79.0±12.94	t=1.711	0.094
HDL (mg/dl)	42.10±3.95	44.02±2.75	t=1.684	0.099
Hormonal parameters				
Serum total testosterone (ng/dl)	4.1 (2.70–5.77)	4.6 (2.70–10.0)	U=162.0	0.129
Serum free testosterone (ng/dl)	92.01±10.99	100.88±23.48	t=1.725	0.092
Serum prolactin (ng/dl)	8.0(3.90–15.0)	7.1(5.03–9.06)	U=153.50	0.085

Intima-media thickness of common carotid artery(mm)				
Left	0.90±0.23	0.51±0.10	t=7.919*	<0.001*
Right	0.86±0.21	0.54±0.08	t=7.342*	<0.001*
Average of two carotids	0.88±0.20	0.53±0.08	t=8.606*	<0.001*
Serum fetuin-A (ng/ml)	1.8 (1.48±5.47)	2.1 (1.77±3.0)	U=2.721*	0.007*
Serum YKL-40 (ng/ml)	606.4 (173.9±2005.6)	263.3 (145.6±649.7)	U=46.0*	<0.001*

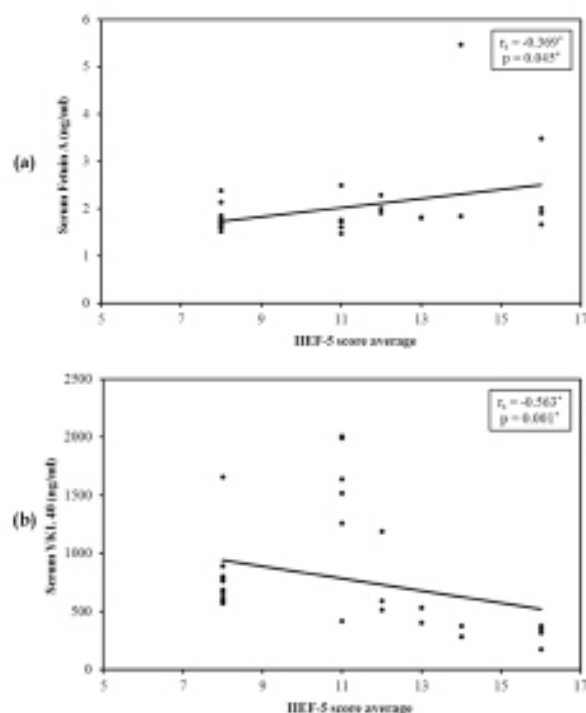
$\chi^2$ :  $\chi^2$  test for comparing between the two groups; FBG, fasting blood glucose; FEP: *P* value for Fisher exact for  $\chi^2$  test for comparing between the two groups; HDL, high-density lipoprotein; LDL, low-density lipoprotein; t, *P*: t and *P* values for Student's t-test for comparing between the two groups; TG, triglycerides; U, *P*: U and *P* values for Mann-Whitney test for comparing between the two groups.

\*Statistically significant at  $P \leq 0.05$

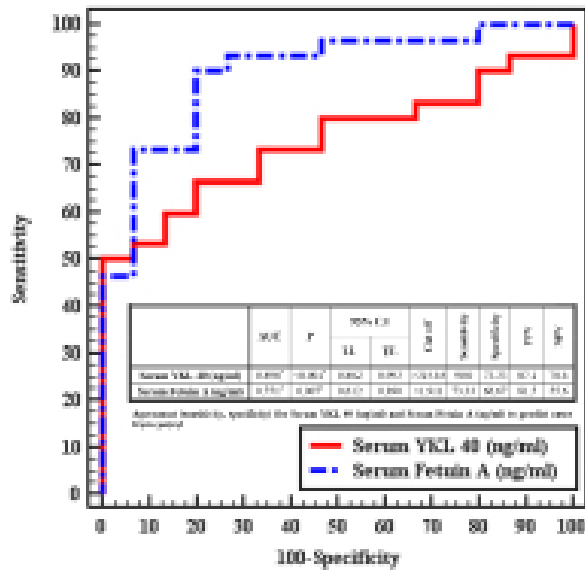
**Table 2:** Relation between severity and different parameters in cases group

	Severity		U	P
	Moderate ID (8-11) (n=58)	Mild to moderate ID (12-16) (n=32)		
Serum YKL-40 (ng/ml)				
Minimum-maximum	419.18-2005.58	173.90-1189.82	19.0*	<0.001*
Mean±SD	988.50±514.90	463.57±268.51		
Median	768.61	374.20		
Serum fetuin-A (ng/ml)				
Minimum-maximum	1.48-2.49	1.67-5.47	37.0	0.004*
Mean±SD	1.78±0.27	2.38±1.14		
Median	1.73	1.91		

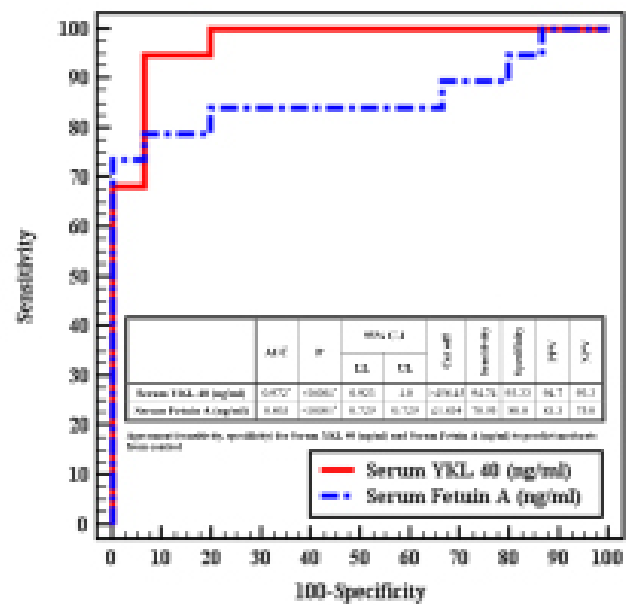
t, *P*: t and *P* values for Student's t-test for comparing between the two groups; U, *P*: U and *P* values for Mann-Whitney test for comparing between the two groups, \* $P < 0.05$



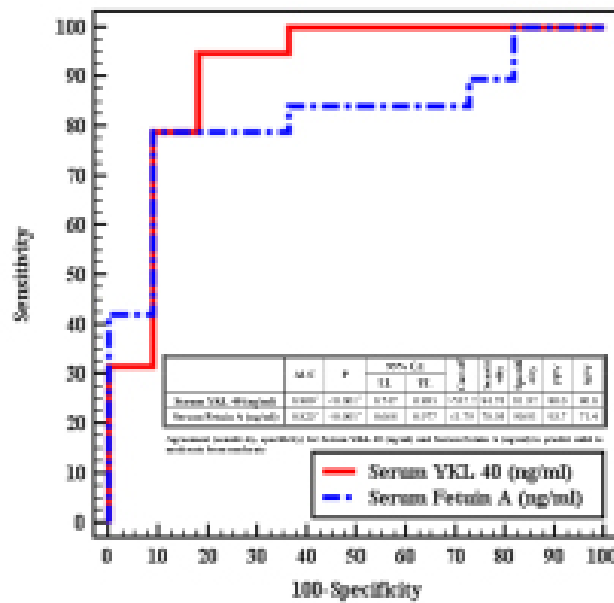
**Fig. 1:** (a) Correlation between serum fetuin-A (ng/ml) and IIEF-5 score average in cases group. (b) Correlation between serum YKL-40 (ng/ml) and IIEF-5 score average in cases group. IIEF-5, International Index of Erectile Function-5.



2a

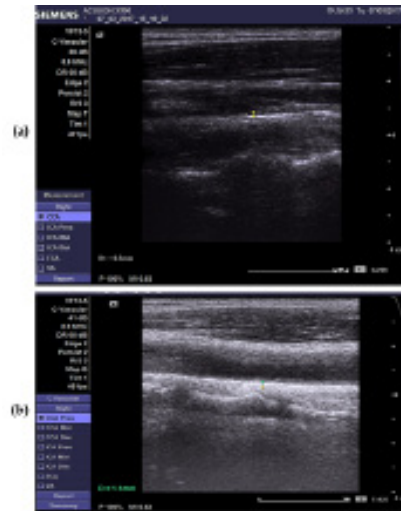


2b



2c

**Fig. 2:** (a) ROC curve for serum YKL-40 (ng/ml) and serum fetuin-A (ng/ml) to predict cases from control and agreement (sensitivity and specificity) for serum YKL-40 (ng/ml) and serum fetuin-A (ng/ml) to predict cases from control. (b) ROC curve for serum YKL-40 (ng/ml) and serum fetuin-A (ng/ml) to predict moderate from control and agreement (sensitivity and specificity) for serum YKL-40 (ng/ml) and serum fetuin-A (ng/ml) to predict moderate from control. (c) ROC curve for serum YKL-40 (ng/ml) and serum fetuin-A (ng/ml) to predict mild to moderate from moderate and agreement (sensitivity and specificity) for serum YKL-40 (ng/ml) and serum fetuin-A (ng/ml) to predict mild to moderate from moderate. ROC, receiver operating characteristic curve.



**Fig. 3** (a) Carotid Doppler ultrasound of the CCA with normal CIMT (left common carotid artery intima-media thickness=0.5 m). (b) Carotid Doppler ultrasound of CCA showing intimal thickness of left and right CCA (left common carotid artery intima-media thickness=1.1 mm). CIMT, carotid intima-media thickness.

**Table 3:** Correlation between different parameters in patient group (n=60)

	Serum fetuin-A (ng/ml)		Serum YKL-40 (ng/ml)		Intima-media thickness of common carotid artery(mm) (average of two carotids)	
	$r_s$	$P$	$r_s$	$P$	$r_s$	$P$
FBG (mg/dl)	-0.184	0.331	0.300	0.107	0.017	0.928
HbA1c (%)	0.195	0.303	-0.069	0.717	-0.229	0.224
Lipid profile						
Serum cholesterol (mg/dl)	0.105	0.580	0.071	0.709	0.188	0.319
TG (mg/dl)	-0.386*	0.035*	0.260	0.166	0.035	0.854
LDL (mg/dl)	-0.136	0.473	0.524*	0.003*	-0.185	0.328
HDL (mg/dl)	0.019	0.919	-0.234	0.214	0.338	0.067
Hormonal parameters						
Serum total testosterone (ng/dl)	0.106	0.577	-0.080	0.674	0.0	0.998
Serum free testosterone (ng/dl)	0.148	0.434	0.036	0.849	-0.242	0.198
Serum prolactin (ng/dl)	0.216	0.252	-0.352	0.056	0.103	0.588
Age (years)	-0.369*	0.045*	0.428*	0.018*	0.035	0.856
IIEF-5 score average	0.462*	0.010*	-0.563*	0.001*	-0.059	0.758
Duration of the disease (years)	0.334	0.071	-0.169	0.372	-0.268	0.152

FBG, fasting blood glucose; HDL, high-density lipoprotein; IIEF-5, International Index of Erectile Function-5; LDL, low-density lipoprotein; rs, Spearman coefficient; TG, triglycerides.

\*Statistically significant at  $P \leq 0.05$ .

## DISCUSSION

Sexual dysfunction of vascular origin is owing to atherosclerosis of the penile arteries. Therefore, sexual dysfunction is more frequently detected in patients at risk of cardiovascular diseases rather than in individuals free of such risk<sup>[17]</sup>.

Similar findings were reported by Karabakan *et al.*<sup>[17]</sup> and Kandeel *et al.*<sup>[18]</sup>, where both studies showed insignificantly variable fasting blood

glucose and lipid profile (cholesterol, TG, LDL, and HDL). This insignificance was intended to exclude other causes that may contribute to endothelial dysfunction (Table 1). Similarly, Karabakan *et al.*<sup>[17]</sup> found an insignificant difference between patients and controls regarding total testosterone and PL serum levels. However, Kandeel *et al.*<sup>[18]</sup> demonstrated significant elevation of testosterone serum level in patients compared with controls.

Atherosclerosis is a systemic process that affects the whole arterial system. The patient's risk-factor profile



(which was excluded in patients) is not the only determinant of endothelial dysfunction. Endothelial function in all stages of the atherosclerotic process is additionally affected by subclinical low-grade inflammation. Carotid arteries can be easily visualized to evaluate the degree of atherosclerosis. CIMT reflects endothelial dysfunctions, thus the risk of CVD as well<sup>[19]</sup>. Our results agreed with Unal *et al.*<sup>[11]</sup>, who concluded in their study that ED correlated with subclinical endothelial dysfunction, assessed by measuring the CIMT, and ED scores correlated inversely with CIMT as well.

Regarding fetuin-A serum level, our results agree with Kandeel *et al.*<sup>[18]</sup> who proved that fetuin-A serum level was found to be significantly lower in cases with severe ED than those with mild or moderate ED. In the same way, Karabakan *et al.*<sup>[17]</sup> also reported that fetuin-A serum level significantly positively correlated with the IIEF-5 score in patients with ED, and this was proved by the present study.

Although this study detected a positive significant correlation between serum fetuin-A and age of the patients (Table 3), Harrison *et al.*<sup>[20]</sup> and Kandeel *et al.*<sup>[18]</sup> failed to prove this significant correlation in their studies, which could be attributed to the small sample size.

Gulhan *et al.*<sup>[21]</sup> could not detect any association between serum fetuin-A and serum testosterone ( $P=0.47$ ), which was compatible with the present study.

Regarding the correlations to the atherogenic lipid profile, the present study proved that serum fetuin-A was only strongly associated with TG serum level (Table 3), and this was also documented by several other studies – to a variable degrees – such as Karabakan *et al.*<sup>[17]</sup> and Yin *et al.*<sup>[22]</sup>, which reported in their studies that fetuin-A was significantly positively correlated with triglyceride and LDL-C plasma levels and negatively correlated with HDL-C. Khalil *et al.*<sup>[23]</sup> and Marechal *et al.*<sup>[24]</sup> also concluded the same results in this their studies.

According to Schoppet *et al.*<sup>[25]</sup>, fetuin-A is a reliable biomarker for endothelial dysfunction in patients with ED and low fetuin-A level could be a participant in the pathogenesis of vascular calcification independent of smoking, hypertension, or renal failure.

Previous studies suggested that microvascular and macrovascular alterations are preceded by endothelial dysfunction, which may be used as an early diagnostic predictor of preclinical target organ damage in both high-risk individuals, in which vascular damage is already established, and low-risk individuals, who will benefit most by early interference<sup>[26]</sup>.

YKL-40 has been linked to the pathogenesis of early and late phases of atherosclerosis, as its level has been demonstrated to be abnormally high in cases with coronary artery disorders, and such elevation is significantly correlated with the severity of the cardiovascular insult<sup>[27]</sup>. Similar to the finding of the present study,

Thomsen *et al.*<sup>[29]</sup> reported an association between the elevated serum cholesterol and LDL and the elevated serum YKL-40 (Table 3).

Like the present study, Yamamori *et al.*<sup>[28]</sup>, Thomsen *et al.*<sup>[29]</sup>, and Sabry *et al.*<sup>[26]</sup> reported a significant association between the serum YKL-40 and age. Aging is one of the main factors that predispose people to endothelial dysfunction. The mechanism of endothelial dysfunction during the aging process is accompanied by imbalance between an increase in the production of cyclooxygenase-derived vasoconstrictor factors and reduction of the expression and activity of e NOS. However, endothelium-derived contracting factors, such as ROS production, ET-1, and cyclooxygenase-derived prostanoids, are increased<sup>[30]</sup>.

Furthermore, the contribution of YKL-40 in the vascular pathology suggests its involvement in the low-grade inflammation which occurs before the onset of the endothelial dysfunction<sup>[5]</sup>. Similarly, Sabry *et al.*<sup>[26]</sup> concluded a significant increase of this marker in early stages of ED patients.

Sabry *et al.*<sup>[26]</sup> showed in their study that the optimum cutoff value of YKL-40 concentration was 50 ng/ml for distinguishing arteriogenic patients with ED from healthy controls, with 85% sensitivity, 68% specificity, and 73% accuracy, whereas in our study, serum YKL-40 had sensitivity of 90.0% and specificity of 73.33% in all patients with ED.

According to the results reported by Kandeel *et al.*<sup>[18]</sup>, serum fetuin-A can predict patients with ED in general with high sensitivity, specificity, and accuracy, and patients with According to the results reported by Kandeel *et al.*<sup>[18]</sup>, serum fetuin-A can predict patients with ED in general with high sensitivity, specificity, and accuracy, and patients with mild ED, with 70% sensitivity, 70% specificity, and 70% accuracy at a cutoff value of greater than or equal to 194.3–266.3 ng/ml. This was compatible with our results, where serum fetuin-A was 73.33% sensitive and 66.67% specific in all patients (moderate and mild to moderate ED) (Fig. 2a), whereas 78.95% sensitivity and 90.91% specificity in patients with mild to moderate ED alone at a cutoff point of less than or equal to 1.79 ng/ml (Fig. 2c).

## CONCLUSION

This study proved that both YKL-40 fetuin-A could be highly sensitive and specific for predicting and diagnosing patients with mild and moderate ED. CIMT measurement by ultrasonography appears to be a useful, simple and noninvasive tool that detects subclinical atherosclerosis in patients with ED who seem to be otherwise healthy.

## CONFLICT OF INTEREST

There are no conflicts of interest.

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