

ORIGINAL ARTICLE

Usefulness of serum fetuin-A level as a marker of erectile dysfunction

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This study aimed to evaluate the correlation between serum levels of fetuin-A and the presence and severity of erectile dysfunction (ED) in Egyptian population. The study was performed on 60 ED patients and 20 age—matched healthy controls. A comprehensive medical history and complete physical examination were obtained and performed in all participants. ED and its severity were assessed via International Index of Erectile Function (IIEF-5). Doppler ultrasound, fasting blood glucose level, complete lipid profile, serum total testosterone (TT) and serum fetuin-A were performed. Our results revealed that there were no statistically significant differences between the ED group and the controls regarding body mass index, fetal bovine serum, cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride (TG). However, IIEF-5 and serum TT levels were significantly lower in ED patients than controls. Regarding serum fetuin-A, our data demonstrated that ED patients had significantly lower serum fetuin-A levels than controls. In addition, patients with severe ED had lower fetuin-A levels than moderate and mild ED ($P < 0.001$). Serum fetuin-A levels are positively correlated with cholesterol, LDL, TG and IIEF-5 and negatively correlated with HDL. In conclusion, serum fetuin-A level could be a potentially useful and sensitive biomarker for ED diagnosis.

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INTRODUCTION

Male erectile dysfunction (ED) is a highly prevalent disorder which significantly increases with aging.¹ ED is known as the failure of a man to develop or keep an adequate erection for a satisfactory sexual performance.² Several factors such as obesity, hypertension, diabetes mellitus, coronary artery disease, alcoholism and atherosclerosis may predispose to ED.³ In addition, medications like antidepressants, β -blockers, and diuretics are commonly associated with ED.^{4,5} Because of the multifactorial nature of ED, there are numerous classification systems for ED. For instance, ED can be classified according to the etiology (diabetic, iatrogenic and traumatic) or according to the pathophysiological mechanism underlying ED (failure to start (neurogenic), failure to fill (arterial) and failure to store (venous)).⁶

Penile erection is a complex neurovascular process which involves a concerted inhibition of sympathetic nervous system and stimulation of parasympathetic nervous system that innervates the penile blood vessels which lead to the release of nitric oxide (NO) from the endothelial cells of vascular and corpus cavernosum.⁷ Decreased production of NO by the lining dysfunctional endothelial cells of the penile vessels causes an inadequate and nonsustainable erection. In addition, the perivascular smooth muscle tissue is rich in the phosphodiesterases that degrade cyclic guanosine monophosphate. The subsequent decrease in guanosine monophosphate level leads to a decrease in the duration of the vasodilatation.⁸

It is well—established that ED is closely related to cardiovascular disease (CVD).⁹ Both ED and CVD share common underlying pathogenic mechanisms and risk factors. Indeed, ED is common in patients having cardiovascular risk factors like aging, smoking, diabetes mellitus, obesity, high blood pressure and dyslipidemia.¹⁰

Fetuin-A, or alpha 2-Heremans Schmid glycoprotein, is a phosphorylated glycoprotein that was found in calf serum by Kai O Pedersen¹¹ in 1944.¹² Although more than 95% of fetuin-A is produced by the liver, some human organs such as the kidneys and the tongue produce a substantial amount of fetuin-A.¹³

It inhibits insulin receptor autophosphorylation and so it is associated with insulin resistance, metabolic syndrome and an increased risk for type 2 diabetes.¹⁴ Mounting evidence demonstrated that Fetuin-A is an important inhibitor of calcium salt precipitation *in vivo* and therefore it may have important roles in bone remodeling and vascular calcifications.¹⁵

It has been reported that decreased serum fetuin-A concentrations promotes the incidence of cardiac fibrosis and calcification and so the development of CVD.¹⁶

Despite the mounting evidence for the potential role of fetuin-A in the development of atherosclerosis and thus ED, which is an early symptom of atherosclerosis, little is known about the relationship between fetuin-A levels and ED in Egyptian patients. Thus, the current study was undertaken to assess the relationship between serum level of fetuin-A and degree and severity of ED in non-diabetic patients free from CVD.

SUBJECTS AND METHODS

Ethics statement

The study protocol was approved by the Ethical Scientific Committee of Benha University. The study was conducted according to the principle of the Helsinki Declaration II. All participants were given a written informed consent.

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Study population

This study included 60 ED patients, recruited from the urology and andrology outpatient clinic during the period from January 2015 to January 2016. Twenty age-matched healthy individuals were recruited and served as a control group. The enrolled patients were stratified into mild, moderate or severe ED group according to the severity of ED (20 patients per each).

The sample size was calculated using the following equation:

$$n = \frac{2 \times \text{s.d.}^2 \times k}{E^2}$$

where *n* is the required sample size, where s.d. stands for the population standard deviation (proposed equal in both groups). The population standard deviation was calculated from a review of the literature. *E* stands for the least variation in the mean of fetuin-A which would be clinically significant. *k* is a magic number which depends on the power and significance levels needed and calculated using special tables at 0.05 level of significance and power of 0.8. Taking (s.d.=68.3, *k*=7.8, *E*=73), so *n*=13.7=14 at least in each group. We increased the sample size in each group up to 20 to avoid differences among populations.

Inclusion criteria

Patients were eligible for enrollment in this study if they were sexually active and accepted to answer the International Index of Erectile Function (IIEF-5) questionnaire based on their sexual history in the last 3 months.

Exclusion criteria

Exclusion criteria for ED patients and control group included the history of hypertension, coronary artery disease, hyperlipidemia, diabetes mellitus end-stage renal disease, thyroid diseases, penile abnormalities and primary or secondary hypogonadism. Patients with neurogenic and major psychiatric disorders, patients receiving ED medications or other medication affect sex hormone within 6 months before the study were also excluded from the study.

Methods

The study participants were subjected to the following:

1. Full medical history taking including the age, history of smoking, sexual dysfunction duration, hypertension and medication history.
2. Full clinical examination including height and weight measurements and calculation of body mass index via dividing weight (in kg) by the square of height (kg m⁻²).

3. Assessment of ED via IIEF-5. Participants were asked to answer five questions without assistance. The assessment was done using a 25-point scale: scores 1–7 points indicate severe ED, 8–11 points a moderate ED, 12–16 points mild-to-moderate ED, 17–21 points mild ED and 22–25 points normal erectile function.¹⁷
4. Doppler ultrasound: ED was diagnosed in patients with the peak systolic velocity < 35 cm s⁻¹ or the end-diastolic velocity > 5 cm s⁻¹.¹⁸
5. 5-A blood sample (~5 ml) was obtained from each participant after fasting for 12 h. The blood samples were obtained under complete aseptic conditions using serum separator tubes. The blood samples were left for ~30 min at room temperature to clot and then centrifuged for 15 min at 1000 g. Serum was separated, aliquoted and kept at ≤ -20 °C until assayed.

The following parameters were assessed:

- Fasting blood glucose.
- Complete lipid profile, including cholesterol, triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).
- Total testosterone (TT): TT was assessed by ST AIA-PACK testosterone using AIA 360 immunoanalyzer.
- Serum fetuin-A was assayed using Quantikine ELISA kit (Quantikine ELISA Catalog Number DFTA00, R&D Systems, Minneapolis, MN, USA) according to the manufacturer’s instructions.

Statistical analysis

Data were analyzed by SPSS-16 software (Spaces, Chicago, ILL Company, Chicago, IL, USA). Data were expressed as a mean ± s.d., median and IQR. Data were tested for normality via the Kolmogorov–Smirnov test, using analysis of variance for normally distributed variables, or Kruskal–Wallis test and Spearman’s correlation coefficient (*ρ*) for non-parametric variables. Cutoff values of fetuin-A were calculated using receiver operating characteristic (ROC) curve with the optimal sensitivity and specificity in the prediction of patients with ED and its degree. Two-sided *P* < 0.05 was considered significant.

RESULTS

This study was conducted on 60 patients with ED and 20 sex and age-matched healthy individuals as a control group. The mean age of our ED patients and control subjects were 45.6 ± 3.2 and 45.7 ± 2.9 years, respectively (*P* = 0.99). Forty-one (68.3%) patients

Table 1. Comparing the studied groups regarding the studied variables

Variable	Severe ED (N = 20)		Moderate ED (N = 20)		Mild ED (N = 20)		Control group (N = 20)		ANOVA	P
	Mean	± s.d.	Mean	± s.d.	Mean	± s.d.	Mean	± s.d.		
Age (y)	45.7	2.7	45.5	3.4	45.7	3.5	45.7	2.9	0.018	0.99
SBP mmHg	129.0	7.18	126.7	7.48	127.5	6.58	124.8	4.43	1.46	0.23
DBP mmHg	83.9	3.66	81.4	4.70	82.4	5.35	80.4	6.09	1.76	0.16
Creatinine mg dl ⁻¹	0.86	0.23	0.89	0.19	0.83	0.15	0.86	0.15	0.34	0.79
BMI (kg m ⁻²)	28.1	2.18	27.8	2.45	26.5	1.58	27.7	2.51	2.14	0.102
FBS (mg dl ⁻¹)	87.5	7.61	86.6	8.15	84.7	12.06	88.7	7.72	0.69	0.56
Cholesterol (mg dl ⁻¹)	211.2	28.7	218.6	22.7	223.0	22.3	210.2	19.04	1.35	0.26
LDL (mg dl ⁻¹)	136.9	13.7	137.8	11.6	140.6	14.5	134.1	15.1	0.77	0.51
HDL (mg dl ⁻¹)	40.3	4.73	40.5	5.90	40.6	6.34	40.4	5.41	0.01	0.99
TG (mg dl ⁻¹)	187.2	49.98	200.2	63.05	207.8	64.46	178.2	37.10	1.15	0.33
IIEF-5	3.1	1.48	9.7	1.08	18.6	1.42	23.5	1.14	74.3 ^a	< 0.001 ^b
T. Testosterone ng dl ⁻¹	411.3	120.8	387.9	128.6	386.8	104.9	526.3	174.5	8.69 ^a	0.034 ^c
Fetuin-A ng ml ⁻¹	158.6	26.84	204.3	50.12	220.8	39.39	321.9	69.87	44.7 ^a	< 0.001 ^b

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; DBP, diastolic blood pressure; ED, erectile dysfunction; FBS, fetal bovine serum; HDL, high-density lipoprotein; IIEF-5, International Index of Erectile Function; LDL, low-density lipoprotein; SBP, systolic blood pressure. ^aKruskal–Wallis test. ^bHighly significant. ^cSignificant.

Table 2. Correlations between serum fetuin-A levels and the studied variables among ED patients

With	Fetuin-A (N = 60)	
	<i>rho</i>	<i>P</i>
Age (y)	0.11	0.40
BMI (kg m ⁻²)	0.232	0.07
FBS (mg dl ⁻¹)	0.099	0.45
Cholesterol (mg dl ⁻¹)	0.533	< 0.001**
LDL (mg dl ⁻¹)	0.468	< 0.001**
HDL (mg dl ⁻¹)	-0.440	< 0.001**
TG (mg dl ⁻¹)	0.640	< 0.001**
IIEF-5	0.568	< 0.001**
T. Testosterone ng dl ⁻¹	0.094	0.47

Abbreviations: BMI, body mass index; ED, erectile dysfunction; FBS, fetal bovine serum; HDL, high-density lipoprotein; IIEF-5, International Index of Erectile Function; LDL, low-density lipoprotein; TG, triglyceride.

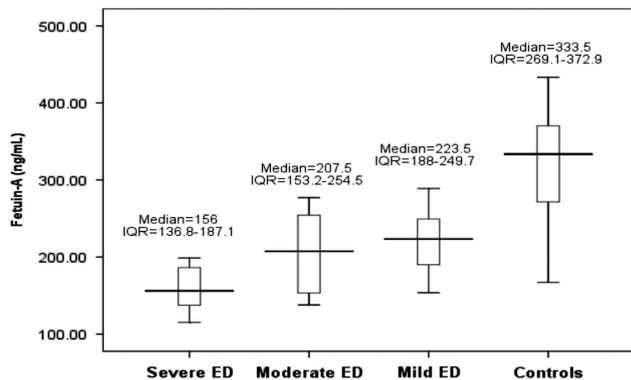


Figure 1. Box plot for the median and IQR of fetuin-A among the studied groups. IQR, inter-quartile range.

and 19 (95%) controls were smokers. Our data revealed that there is no significant difference between the patient and control groups regarding body mass index, fetal bovine serum, cholesterol, LDL, HDL and TG. Our results demonstrated also that the IIEF-5 score and serum T. Testosterone level were significantly different in patients compared with the controls ($P < 0.001$ and 0.034, respectively). Concerning the serum fetuin-A level, our results showed that fetuin-A is significantly lower in ED patients than the control ($P < 0.001$). Interestingly, the extent of fetuin-A decrease correlates with the severity of ED. As indicated in Table 1, the levels of fetuin-A were 158.6 ± 26.84 , 204.3 ± 50.12 ; and 220.8 ± 39.39 ng ml⁻¹, in patients with severe, moderate and mild ED, respectively.

As demonstrated in Table 2, serum fetuin-A levels were positively correlated with cholesterol, LDL, TG, and IIEF-5 ($P < 0.001$) and negatively correlated with HDL ($P < 0.001$). There were no significant correlations found between serum fetuin-A level and age, body mass index, fetal bovine serum or T. Testosterone (Figure 1).

ROC analysis of the data showed that the best cutoff value of serum fetuin-A was valued ≤ 266.3 ng ml⁻¹. This value could predict patients with ED, with an area under the curve of 0.93 and a confidence interval of (0.86–0.999); $P < 0.001$. Serum fetuin-A had a sensitivity of 95%, specificity of 80%, positive predictive value of 93.4%, negative predictive value of 84.2% and accuracy of 91.3% (Figure 2).

As depicted in the second ROC curve, serum fetuin-A can predict patients with mild ED at the cutoff point of

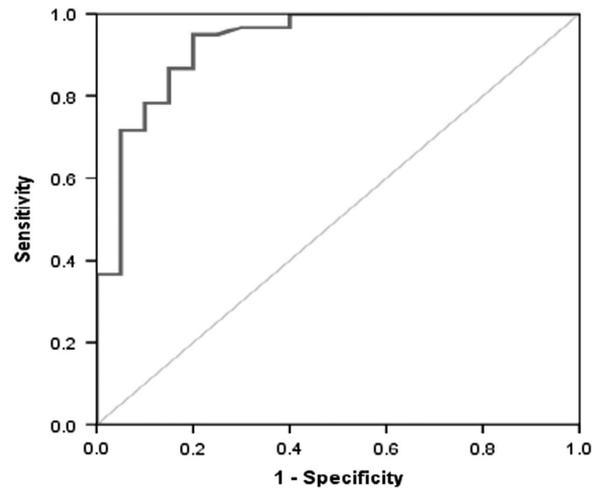


Figure 2. ROC curve for the performance of fetuin-A in prediction of patients with ED. ED, erectile dysfunction.

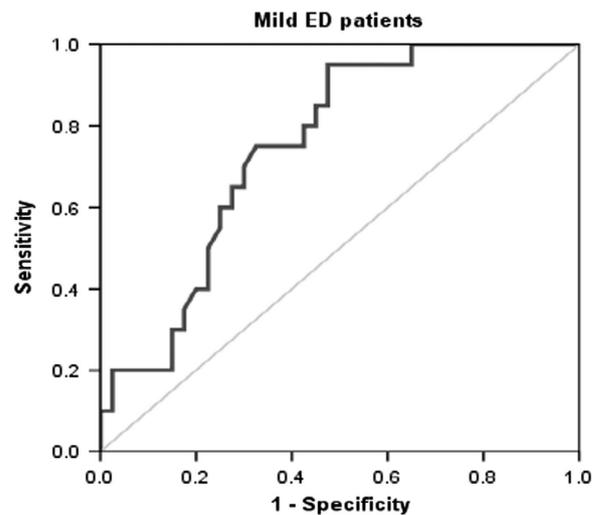


Figure 3. ROC curve for the performance of fetuin-A in prediction of patients with mild ED. ED, erectile dysfunction.

≥ 194.3 – 266.3 ng ml⁻¹ with an area under the curve of 0.75 and a confidence interval of (0.63–0.87); $P = 0.002$ (S). Serum fetuin-A had a sensitivity of 70%, specificity of 70%, positive predictive value of 53.8%, negative predictive value of 82.4% and accuracy of 70% (Figure 3).

The third ROC curve shows that serum fetuin-A can predict patients with severe ED at the cutoff point of < 185.3 ng ml⁻¹ with an area under the curve of 0.83 and a confidence interval of (0.72–0.93); $P < 0.001$. Serum fetuin-A had a sensitivity of 75%, specificity of 70%, positive predictive value of 55.6%, negative predictive value of 84.8% and accuracy of 71.7% (Figure 4).

DISCUSSION

ED is a common condition which interferes with quality of life of the affected persons. World Health Organization states that sexual wellbeing is essential to the physical and emotional health of individuals, couples, families, and the social and economic improvement of countries.¹⁹

Endothelial dysfunction is a common underlying factor in both ED and coronary artery disease. Endothelial dysfunction is

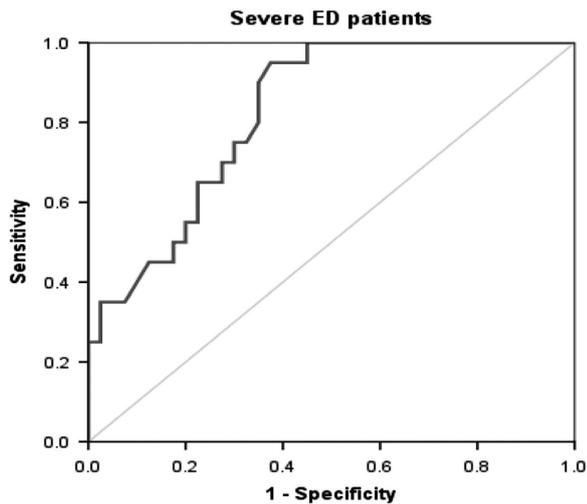


Figure 4. ROC curve for the performance of fetuin-A in prediction of patients with severe ED. ED, erectile dysfunction.

characterized by defective vasodilation, decreased NO production and increased permeability to plasma components such as LDLs. These effects lead to vasoconstriction, platelet aggregation, and leukocyte adhesion.²⁰

Fetuin-A is known as a calcification inhibitor which contributes to the development of inflammation process and atherosclerosis.²¹

Fetuin-A has multiple pathophysiological functions. The increase or the decrease of the fetuin-A level is linked to the pathogenesis of multiple disorders such as atherosclerosis.²² Naito et al.²³ found that fetuin-A contributes to atherosclerosis through a proinflammatory effect on endothelial cells of the human umbilical vein. Fetuin-A stimulates macrophage to form foam cell and trigger proliferation and production of collagen in human aortic smooth muscle cells. Decreased serum level of fetuin-A is linked to defective cardiac functions. Fetuin-A has an important role in promoting cardiac fibrosis and calcification and therefore the development of CVD.²⁴ Kadoglou et al.²⁵ found that low fetuin-A levels can be considered as a valuable predictor of cardiovascular disorders. Also, Sun et al.²⁶ concluded that serum fetuin-A can be a risk biomarker in patients with type 2 diabetes mellitus.

A study done by Schoppet et al.²⁷ revealed that low fetuin-A level may have a role in vascular calcification independent of renal impairment, smoking, and hypertension. These authors concluded that patients with severe abdominal aortic calcifications had significantly lower serum fetuin-A levels.

We aimed in our study to investigate whether fetuin-A could be used as a sensitive and reliable diagnostic biomarker for ED and to establish the relationship between fetuin-A levels and the severity of ED.

The study revealed that serum fetuin-A level was significantly lower in patients with ED than in normal control subjects ($P < 0.001$). Furthermore, fetuin level was lower in severe ED patients ($158.6 \text{ ng ml}^{-1} \pm 26.84 \text{ s.d.}$) than mild and moderate ED patients (204.3 ± 50.12 and $220.8 \pm 39.39 \text{ ng ml}^{-1}$, respectively). This finding agrees with the study done by Karabakan et al. who found a statistically significant difference in serum fetuin-A level among ED patients and controls. They also found that fetuin-A level was significant low in patients with severe ED ($156.7 \pm 42.7 \mu\text{g ml}^{-1}$) compared to patients with mild or moderate ED (202.4 ± 71.5 , $240.2 \pm 68.3 \mu\text{g ml}^{-1}$, respectively).²⁸ In addition, Karabakan et al.²⁸ reported that serum fetuin-A levels are positively correlated with the level of lipid profile (cholesterol,

LDL, TG) and IIEF-5 score ($P < 0.001$). On the other hand, serum fetuin-A was negatively correlated with HDL ($P < 0.001$). Serum fetuin-A levels are strongly associated with the atherogenic lipid profile (higher levels of LDL and TG, and lower levels of HDL). This is inconsistent with the study done by Yin et al.²⁹ who found significant positive correlations between plasma levels of fetuin-A and LDL—C and triglyceride, but negative correlation with HDL-C.

Khalil and Faizehalkuobaili³⁰ also found that serum fetuin-A was positively correlated with total cholesterol ($r = 0.417$, $P < 0.01$), triglycerides ($r = 0.295$, $P < 0.02$) and LDL ($r = 0.388$, $P < 0.01$), while it was negatively correlated with HDL ($r = -0.35$, $P < 0.01$).

Also, Marechal et al.³¹ found a significant positive correlation between fetuin-A and plasma triglyceride ($P = 0.012$) and total cholesterol ($P < 0.0001$) levels.

In the current study, serum fetuin-A levels showed a significant positive correlation with IIEF-5 ($P < 0.001$).

The present study demonstrates that there was no correlation between serum fetuin-A levels and T. Testosterone ($P = 0.47$). This finding is in harmony with the study done by Gulhan et al.³² who reported that serum fetuin-A levels did not correlate with elevated testosterone levels in polycystic ovary syndrome cases.

In this study, ROC curve analysis suggested that the best cutoff value of serum fetuin-A is $\leq 266.3 \text{ ng ml}^{-1}$. This value could predict patients with ED with a sensitivity of 95% and specificity 80%. It also could predict patients with mild ED at the cutoff value of $\geq 194.3 - 266.3 \text{ ng ml}^{-1}$ with a sensitivity of 70% and specificity 70%. It could also predict patients with severe ED at the cutoff value of $< 185.3 \text{ ng ml}^{-1}$ with a sensitivity of 75% and specificity 70%.

CONCLUSION

This study documented the presence of an association between fetuin-A and ED. Fetuin-A could be useful and sensitive biomarkers that have a high specificity for the prediction and diagnosis of ED.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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