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Research Article

Relationship of serum Fetuin-A with metabolic and vascular parameters in patients with prediabetes and type 2 diabetes mellitus

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Abstract

Background: Fetuin-A is a multifunctional liver-derived glycoprotein that is associated with insulin resistance and might play a role in the pathogenesis of prediabetes and type 2 diabetes (T2DM).

Objective: This study evaluated the relationship of Fetuin-A with metabolic and vascular parameters in patients with prediabetes and T2DM.

Materials and methods: total 120 obese patients were included. They were divided into three groups: group 1 – without carbohydrate disturbances, group 2 – with prediabetes and group 3 – with type 2 diabetes mellitus.

Results: Higher Fetuin-A serum levels were observed in patients with prediabetes and T2DM compared to those with normoglycemia. Fetuin-A ≥821 mcg/ml increased the risk for T2DM 32-fold. Additionally, we found positive correlations between Fetuin-A, vibration perception threshold and toe-brachial index and a negative correlation with neuropathy disability score.

Conclusion: Fetuin-A could be predictive for incidents of prediabetes and T2DM.

Keywords

Fetuin-A, prediabetes, type 2 diabetes mellitus, vascular parameters

Introduction

Type 2 Diabetes mellitus (T2DM) is a worldwide pandemic which can lead to damage and failure of different organs, especially the nerves, eyes, kidneys, heart, and blood vessel. Cardiovascular diseases (CVD) are the most common cause of mortality in diabetic patients, as they account for 52% of deaths in T2DM (Morrish et al. 2001). According to the 2019 International Diabetes Federation (IDF) statistics, the global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), and it is expecting to rise up to 10.2% (578 million) by 2030 and 10.9%

(700 million) by 2045. One in two (50.1%) people living with diabetes are not diagnosed (Saeedi et al. 2019). Prediabetic states, characterized by impaired fasting glycaemia (IFG) or impaired glucose tolerance (IGT), have also been shown to be associated with CVD morbidity and mortality as well as with a number of microvascular complications (Gerstein et al. 2005). The global prevalence of impaired glucose tolerance is estimated to be 7.5% (374 million) in 2019 and predicted to reach 8.0% (454 million) by 2030 and 8.6% (548 million) by 2045 (Saeedi et al. 2019) it is therefore important to have a better understanding of the pathophysiology, in order to identify new approach to tackle or prevent the development of micro- and macrovascular complications early on.

Hepatokines, like liver-derived hormones, can regulate systemic energy metabolism and insulin sensitivity through integrated organ crosstalk and could be involved in the development of T2DM and prediabetes. Fetuin-A, also known as alpha-2-Heremans-Schmid glycoprotein (64 kDa), is produced mainly by the liver. In humans, the fetuin A gene is located on chromosome 3q27, which has been identified as a suspected locus for T2DM and metabolic syndrome (MetS) (Mori et al. 2006). Fetuin-A is a multifunctional hepatokine that is associated with obesity, insulin resistance and non-alcoholic fatty liver disease (Stefan et al. 2006; Yilmaz et al. 2010; Haukeland et al. 2012). It is also considered a biomarker for neurovegetative diseases, as well as an indicator of cardiovascular risk, endothelial dysfunction and subclinical atherosclerosis (Mori et al. 2012; Dogru et al. 2013). It has been suggested that Fetuin-A exacerbates insulin resistance by inhibiting the insulin receptor tyrosine kinase, reducing the adiponectin expression, and increasing the production of some inflammatory cytokines (Hennige et al. 2008). It inhibits phosphorylation of the insulin receptors in the liver and muscles which leads to an impairment of insulin signaling and development of insulin resistance (Hennige et al. 2008). These findings suggest that fetuin-A may play a critical role in the regulation of insulin sensitivity. Fetuin-A-knockout mice demonstrated improved insulin sensitivity and resistance to weight gain induced by high-fat diet, whereas treatment with fetuin-A exerted the opposite effects (Heenige et al. 2008) Human studies suggest that circulating fetuin-A levels were positively associated with T2DM and MetS as its role in the pathogenesis of prediabetes and T2DM has been discussed (Ix et al. 2006).

The objective of this study was to investigate the relationship of fetuin-A with basic metabolic and micro- / macrovascular parameters in patients with prediabetes and T2DM.

Materials and methods

A total of 120 obese patients (34 males, 86 females; mean age 53.4±9.3 years, from 45 to 74 years old) recruited in a tertiary University clinic of Endocrinology participated in the study. Subjects were included in the study if they had obesity (BMI ≥ 30 kg/m^2). Criteria for exclusion were as follows: liver dysfunction (any of the hepatic enzymes >3 times the upper limit of normal); chronic kidney disease (eGFR estimated by CKD-EPI calculation <60 ml/min/1.73m^2), heart failure or ischemic heart disease; any proven neoplastic disease. The subjects were divided into three groups. Group 1 included 40 patients without carbohydrate disturbances, group 2 was with prediabetes (n=40) and group 3 with T2DM (n=40). For the purpose of this study, prediabetes was defined specifically as impaired glucose tolerance (IGT) and/or impaired fasting glycemia (IFG). According to the American Diabetes Association (ADA), IGT is defined as a 2-hour plasma glucose value in the 75-gram oral glucose tolerance test (OGTT) from ≥140 mg/dL (≥7.8 mmol/L) to ≤199 mg/dL (≤11.0 mmol/L). IFG is defined as a fasting plasma glucose from 100 mg/dL (≥5.6 mmol/L) to 125 mg/dL (≤6.9 mmol/L). T2DM was defined for the purpose of this study as fasting plasma glucose ≥ 7 mmol/L or 2-hour plasma glucose value during OGTT ≥ 11.1 mmol/L. The project was approved by the University ethics committee for clinical studies (Protocol KP-06N23/11/18.12.2018) and all included patients signed an informed consent for participation in the study. The following study methods were used: Anthropometric parameters as weight (kg), height (m), body mass index (BMI; kg/m^2), waist and hip circumference (cm), arterial blood pressure (mmHg) were measured by a standard method. Waist-to-hip ratio (WHR) and waist-to-stature ratio (WSR) were calculated. Visceral adiposity index (VAI) was calculated using the established formula: VAI = [WC/(36.85+ (1.89 · BMI))] · [triglycerides (TG)/0.81] · [1.52/high-density lipoproteins (HDL)] for females and VAI = [(WC/(39.68+(1.88 ·BMI))] · (TG/1.03) · (1.31/HDL) for males. VAI was validated as a tool for assessment of cardiometabolic risk by means of magnetic resonance imaging and euglycemic hyperinsulinemic clamp (Amato et al. 2010). Percentage body fat (%) was measured by means of Body Impedance analysis (BIA) with TANITA-TM TBF-215 GS Body Composition Analyzer in fasting state. A standard OGTT with measurement of glucose and insulin on 0 minute (glucose 0, insulin 0), 60 minutes (glucose 60, insulin 60), and 120 minutes (glucose120, insulin120) was performed. Homeostatic model assessment for IR (HOMA-IR) was calculated using the following formula: HOMA-IR = fasting plasma glucose (mmol/l)*fasting serum insulin (mIU/ml)/22.5. IR was defined as a value of HOMA-IR >2.5. Metabolic syndrome was diagnosed following the IDF criteria (Alberti et al. 2009).

To assess subclinical atherosclerosis and peripheral artery disease, we used the following noninvasive methods: (1) Intima-media thickness (IMT) measurement of the common carotid artery by Cardio Health Station (Panasonic Corporation, Osaka, Japan); (2) ankle-brachial index (ABI, represents the ratio between the systolic blood pressure at the ankle and the upper arm) and toe-brachial index (TBI) (Tehan et al. 2016). The TBI is a ratio of the

systolic toe pressure divided by the highest systolic brachial pressure. Systolic toe pressure can be measured by placing an appropriately sized occlusive pneumatic cuff (between 15 and 25 mm) around the base of the proximal first or second toe and a photoplethysmography (PPG) probe affixed to the distal pulp of the toe with adhesive tape (Tehan et al. 2016). To detect distal small fiber neuropathy we measured sweat function (ANR - autonomic neuropathy risk), using Sudoscan TM (Impeto Medical, Paris, France) (Mao et al. 2017). We also evaluated peripheral somatic sensory neuropathy by using vibration perception threshold (VPT) assessed with a biothesiometer (Mao et al. 2017). Neuropathic deficits in the feet were determined using the neuropathy disability score (NDS), derived from inability to detect pinprick sensation (using Neurotip), vibration (using 128-Hz tuning fork), and differences in temperature sensation (using warm and cool rods) plus Achilles reflex (using tendon hammer) (Dasgupta et al. 2010).

Measurement of serum Fetuin-A levels was performed by enzyme-linked immunosorbent assay (BioVender Laboratory Medicine, Brno, Czech Republic).

For statistical analysis, the data were processed using the statistical package IBM SPSS Statistics version 25.0. Data are presented as mean ± SD. The following statistical methods were applied: variation, descriptive and graphic analyses; Kolmogorov-Smirnov's and Shapiro-Wilk tests; analysis of variance for two independent samples; Mann-Whitney's nonparametric test for two independent samples; correlation analysis and receiver operating characteristic (ROC) curve analysis. The level of significance for rejecting the null hypothesis was $p < 0.05$.

Results

The clinical and biochemical characteristics of the patients divided by groups are shown in Tables 1, 2. The three groups did not differ with regards to age and main anthropometric parameters, excluding VAI, for which we observed significantly higher values in patients with T2DM. Using correlation analysis, Fetuin-A correlated positively with weight (r=0.330; $p < 0.001$), BMI (r=0.283; p=0.002), waist (r=0.341; p=0.001), glucose 0 min (r=0.285; p=0.025), glucose 60 min (r=0.283; p=0.007), insulin 0 min (r=0.279; $p = 0.008$), insulin 60 min (r=0.379; p<0.001), insulin 120 min (r=0.397; p<0.001) of OGTT, AST (r=0.280; p=0.004) and ALT (r=0.336; p<0.01). In patients with prediabetes and T2DM Fetuin-A serum levels were higher compared to those with normoglycemia (933.8±366.7; 909.1±302.9 vs 621.3±95.0 mcg/ml, p <0,05) (Fig. 1).

Table 1. Comparative analysis between the groups according to age and anthropometric parameters.

Parameters	Group 1 Obesity	Group 2 Prediabetes	Group 3 Type2 Diabetes
Age (years)	53.7±7.9	51.9±10.3	54.6±9.5
Weight (kg)	93.6±11.1	95.0±16.8	100.9±28.3
BMI (kg/m^2)	35.2±3.5	35.3±5.4	34.8±8.7
% Fat mass	40.3±7.2	39.6±6.1	35.9±8.9
WHR	0.89±0.09	0.90±0.08	0.95±0.09
WSR	0.64±0.05	0.66±0.08	0.64±0.09
VAI	3.6±0.8	4.6±1.3	**6.4±3.5*#**

* p<0,05 between groups 1 and 3;
# p<0,05 between groups 2 and 3;
BMI - body mass index; WHR - waist-to-hip ratio; WSR - waist-to-stature ratio; VAI - visceral adiposity index.

Table 2. Comparative analysis of the studied parameters in the considered groups of patients.

Parameters	Group 1 – obesity			Group 2 – Prediabetes			Group 3 – Type 2 Diabetes			p		
	n	X	SD	n	X	SD	n	X	SD	1–2	1–3	2–3
SBP (mmHg)	40	128.55^{ac}	19.81	39	124.87^{a}	16.66	39	133.74^{bc}	18.04	0.473	0.094	**0.022**
DBP (mmHg)	40	81.33^{a}	11.47	39	80.69^{a}	10.86	39	83.00^{a}	8.90	0.968	0.395	0.312
TC (mmol/L)	39	5.58^{a}	1.43	39	5.61^{a}	1.16	35	5.42^{a}	1.48	0.606	0.478	0.258
HDL (mmol/L)	40	1.42^{a}	0.28	37	1.24^{b}	0.34	36	1.07^{c}	0.34	**0.010**	**<0.001**	**0.044**
LDL (mmol/L)	40	3.52^{a}	1.25	37	3.40^{ac}	1.11	36	2.94^{bc}	1.09	0.899	**0.047**	0.078
VLDL (mmol/L)	40	0.63^{a}	0.31	36	1.00^{b}	0.57	37	1.48^{b}	1.22	**<0.001**	**<0.001**	0.127
TG (mmol/L)	40	1.38^{a}	0.68	38	2.14^{b}	1.24	38	3.22^{b}	2.65	**<0.001**	**<0.001**	0.091
AST (U/L)	40	18,.83^{a}	8.38	39	21.21^{b}	6.84	34	36.03^{b}	29.07	**0.014**	**0.007**	0.093
ALT (U/L)	40	21,35^{a}	10.36	39	27.87^{b}	16.51	39	42.95^{b}	33.13	**0.041**	**0.003**	0.102
GGT (U/L)	40	33.20^{a}	36.60	37	42.24^{b}	32.30	35	93.89^{c}	125.23	**0.044**	**<0.001**	**0.010**
Creatinine (mmol/L)	40	69.65^{a}	12.92	39	73.77^{a}	13.60	39	77.87^{a}	20.14	0,172	0.094	0.576
Glu 0 (mmol/L)	40	5.39^{a}	0.44	39	6.16^{b}	0.50	31	11.03^{c}	5.02	**<0.001**	**0.001**	**0.021**
Glu 60 (mmol/L)	39	7.87^{a}	2.01	39	10.89^{b}	2.77	12	13.01^{c}	4.52	**<0.001**	**<0.001**	**0.008**
Glu 120 (mmol/L)	39	5.86^{a}	1.19	38	7.74^{b}	1.64	11	10.86^{c}	3.75	**<0.001**	**<0.001**	**0.007**
Insulin 0 (mU/mL)	40	12.80^{a}	5.60	39	20.75^{b}	11.61	11	34.25^{b}	23.70	**<0.001**	**<0.001**	0.056
Insulin 60 (mU/mL)	39	87.45^{a}	54.27	38	146.53^{b}	90.00	11	171.84^{b}	119.42	**0.001**	**0.010**	0.684
Insulin 120 (mU/m)	39	47.37^{a}	28.69	37	121.74^{b}	83.48	11	136.40^{b}	112.31	**0.026**	**0.002**	0.741
HOMA-IR	40	3.10^{a}	1.48	32	5.67^{b}	3.26	8	11.85^{b}	10.68	**<0.001**	**0.029**	0.105

* same letters horizontally mean no significant difference; different letters - the presence of such (p<0.05);
SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high density lipoproteins; LDL, low density lipoproteins; TG,triglycerides; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase; Glu 0, glucose at the zero minute; Glu60: glucose at the sixties minutes; Glu120: glucose at the one hundred and twenty minutes; Insulin0: insulin at the zero minute; Insulin60: insulin at the sixties minutes; Insulin120: insulin at the one hundred and twenty minutes; HOMA-IR: homeostatic model assessment of insulin resistance.

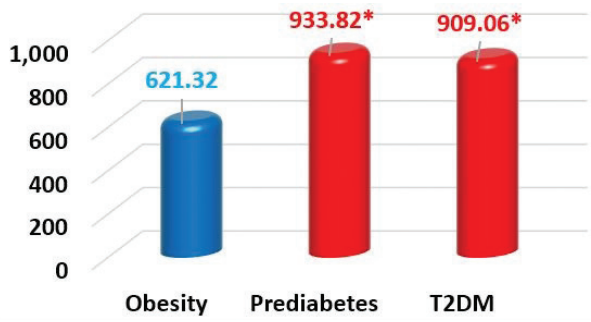

Figure 1. Levels of Fetuin-A between the groups. *p < 0.001.

A multiple binary logistic regression analysis was conducted to assess whether Fetuin-A has any predictive value for determination of risk for prediabetes, T2DM and MetS. The ROC curves method was applied to find a threshold value (Figs 2, 3). Fetuin-A levels ≥ 805 mcg/ml had the best discriminative value for differentiating patients with obesity and prediabetes (Table 3). Patients with circulating serum Fetuin-A ≥805 mcg/ml had a 15-fold higher risk of prediabetes (Table 4). Fetuin-A ≥ 821 mcg/ml had the best value to differentiate subject with T2DM (Table 5). Fetuin-A levels ≥821 mcg/ml increased the risk for T2DM approximately 32 times (OR 31.667, 95% CI 6.659–150.598, p < 0.001). Fetuin-A values ≥824 mcg/ml differentiated subject with MetS (AUC=0.632, p=0.040, sensitivity of 42%, specificity 81% and precision 51%). Fetuin-A levels ≥824 mcg/ml were associated with a 4fold higher risk for MetS (OR 4.107, 95% CI 1.304–12.932, p=0.016).

From the studied parameters for micro- and macrovascular risk, we found positive correlations of Fetuin-A with vibration perception threshold and toe-brachial index, as well as a negative correlation with neuropathy disability score (Table 6). There was no correlation of Fetuin-A with ankle-brachial index, intima-media thickness and autonomic neuropathy risk.

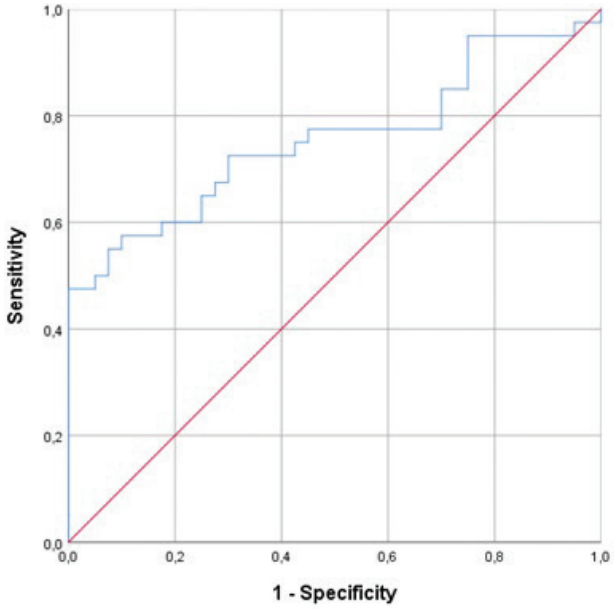

Figure 2. ROC curve of Fetuin-A (AUC=0.756, p<0.001) to determine a threshold value for differentiation between patients with obesity and prediabetes.

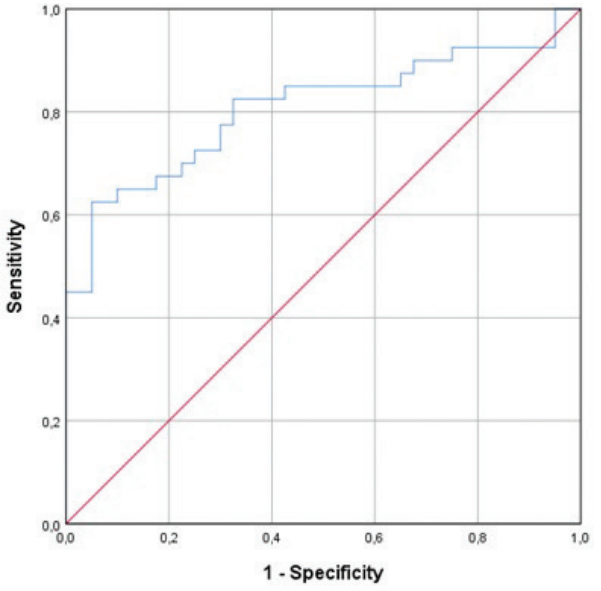

Figure 3. ROC curve of Fetuin-A (AUC=0.807, p < 0.001) to determine a threshold value for differentiation between patients with obesity and T2DM.

Discussion

The results of this study have shown higher Fetuin-A levels in the patients with prediabetes and T2DM in comparison with those without any glycemic disorders. We have also demonstrated that Fetuin-A levels correlated positively with important micro- and macrovascular indicators. This is the first study that evaluates the association between serum Fetuin-A concentrations and the whole spectrum of the carbohydrate metabolism - through prediabetes and type 2 diabetes mellitus, and its relationship with important vascular parameters. Several studies reported that serum Fetuin-A concentrations are significantly higher in patients with T2DM which is associated with its proposed mechanism of action leading to suppression of the insulin receptor tyrosine kinase (Ix et al. 2006). Although the effect of Fetuin-A on insulin sensitivity has been well established, little is known about the mechanisms regulating its expression. Two studies report that palmitate stimulates nuclear factor-κB binding to the Fetuin-A promoter in order to increase the expression of Fetuin-A. Also high glucose enhances Fetuin-A expression through activation of

Table 3. Threshold levels of Fetuin-A and criteria for validation when differentiating patients with and without prediabetes and values of the criteria for validation of screening tests.

Parameter	Threshold value	Sensitivity	Specificity	Positive predictive value (%)	Negative predictive value (%)	Precision(%)
Fetuin- A	≥805	55	93	88	67	74

Table 4. Odds ratio and 95% confidence intervals of the studied predictors for development of prediabetes.

Parameter	Comparison	OR	Lower limit	Upper limit	P value
Fetuin- A	≥ 805 / < 805	15.074	3.982	57.069	< 0.001

ERK1/2 (Takata et al. 2009; Dasgupta et al. 2010). Another study suggests the involvement of endoplasmic reticulum stress induced by high glucose and palmitate significantly increases the expression of Fetuin-A and further contributes to the development of insulin resistance in human hepatoma cell line (HepG2) and in diabetic mice with high-fat diet induced insulin resistant (Ou et al. 2012). Therefore, it is plausible that in the presence of insulin resistance, the secretion of Fetuin-A might be up-regulated indirectly by the increased circulating glucose and free fatty acids and this leads to further deterioration of insulin resistance by Fetuin-A (Ou et al. 2012). In an observational study with 3075 elderly individuals (aged between 70 and 79 years), the authors established an independent association of high circulating Fetuin-A levels with incident of diabetes (Ix et al. 2008). In animal studies with fetuin-A-null mice, the models were protected against insulin resistance and showed higher insulin receptor autophosphorylation and tyrosine kinase activity in skeletal muscle and liver compared to wild-type mice (Mathews et al. 2006; Hennige et al. 2008). Despite these convincing data, not all studies have found an association between Fetuin-A and insulin resistance among established type 2 diabetic patients as some of the data are quite contradictory (Mori et al. 2006) do not establish statistically significant differences of Fetuin-A levels between nondiabetic and type 2 diabetic subjects. Serum Fetuin-A levels were significantly correlated with log(HOMA) in nondiabetic individuals (r=0.197, p =0.014) (Mori et al. 2006). In the same study the authors demonstrated the independent impact of Fetuin-A on insulin resistance in nondiabetic subjects. In human studies, serum Fetuin-A levels were associated with various types of metabolic complications. Fetuin-A levels correlated positively with BMI, visceral fat and waist circumference, as demonstrated by two previous cross-sectional studies (Takata et al. 2009). In addition, higher Fetuin-A levels are predictive for MetS and insulin resistance in nondiabetic, prediabetic and diabetic subjects (Ix et al. 2008; Ishibashi et al. 2010).

In our study, where all patients were obese, we also found positive associations of Fetuin-A levels with weight, waist circumference and BMI, as well as with some main metabolic indicators including blood glucose, insulin, HOMA-IR, AST, ALT. Moreover, we established that higher Fetuin-A was predictive for T2DM and prediabetes.

It is well established that CVD are the most common cause of mortality in diabetic patients, which accounts for 52% of deaths in T2DM (Morrish et al. 2001). Patients with T2DM are likely to have multiple atherosclerotic cardiovascular disease (ASCVD) risk factors (including dyslipidemia and hypertension), each of which mediates an increase in risk of both ASCVD and non-ASCVD. Type 1 diabetes mellitus, T2DM and prediabetes are independent risk factors for ASCVD, increasing its risk about two-fold, depending on the population and therapeutic control (Sarwar et al. 2010). Previous studies indicate a close bidirectional relationship between Fetuin-A and CVD. An association of Fetuin-A with the risk of myocardial infarction and ischemic stroke has been established, regardless of standard risk factors. It has not yet been decided whether Fetuin-A could be considered a potential biomarker of cardiovascular risk. In a case-cohort study, Weikert et al. showed that patients with higher Fetuin-A concentrations had 4-fold increased risk for myocardial infarction and ischemic stroke. Furthermore, a positive correlation of Fetuin-A with arterial stiffness and increased intima-media thickness have been observed in healthy subjects (Weikert et al. 2008). Many authors found that serum fetuin-A level may be a sensitive indicator for macrovascular complications in diabetic patients (Singh et al. 2012). On the other hand, some clinical studies have indicated the opposite trends- lower serum Fetuin-A levels have been associated with the presence of peripheral artery disease (PAD) in diabetics, increased arterial stiffness, atherosclerotic plaque calcification and progression of cardiovascular disease (Reinehr et al. 2008; Zhao et al. 2013). Hence, it is likely that both high and low Fetuin-A might cause cardiovascular dysfunction. This dual functionality of Fetuin-A needs further evaluation. Recent studies have revealed that long-term complications of diabetes could manifest even at the prediabetic state. The macrovascular disorders associated with prediabetes include CVD, stroke and peripheral arterial disease. In fact, the traditional CVD risk factors (dyslipidemia, obesity, hypertension) are quite prevalent among individuals with prediabetes (Stacey et al. 2015; Huang et al. 2016).

Table 5. Threshold levels of Fetuin-A and criteria for validation when differentiating patients with and without T2DM and values of the criteria for validation of screening tests.

Parameter	Threshold value	Sensitivity	Specificity	Positive predictive value (%)	Negative predictive value (%)	Precision(%)
Fetuin- A	≥ 821	63	95	93	72	79

Table 6. Correlation analysis between micro- / macrovascular parameters and Fetuin-A.

Parameters	Fetuin-A
ABI	-0.076
IMT	0.091
VPT	0.208*
NDS	-0.300**
ANR	-0.118
TBI	0.225*

* - p < 0.05, ** - p < 0.01, *** - p < 0.001

ABI - Ankle-brachial index; IMT - Intima-media thickness; VPT - Vibration perception threshold; NDS - Neuropathy disability score; ANR - Autonomic neuropathy risk; TBI - Toebrachial index.

Further we evaluated the relationship of Fetuin-A with some main macrovascular risk parameters in patients with obesity and/or prediabetes and/or T2DM, such as: ankle-brachial index, intima-media thickness and toe-brachial index. We found positive correlations between Fetuin-A, vibration perception threshold and toe-brachial index. The data in the literature on the relationship between Fetuin-A and microvascular risk factors in patient with prediabetes and T2DM is still insufficient. A meta-analysis reported pooled data on the association between circulating fetuin-A levels and all-cause mortality in patients with chronic kidney disease (CKD) (Zhou et al 2019). Data suggested that CKD patients with Fetuin-A levels in the lowest tertile had 92% greater risk of all-cause mortality compared to those in the highest tertile. In a subgroup analysis, the significant association between low Fetuin-A levels and higher risk of mortality was observed only among patients on dialysis. We also evaluated the relationship of Fetuin-A with some indicators of microangiopathy, including vibration perception threshold, neuropathy disability score and autonomic neuropathy risk. The results showed a positive correlation of Fetuin-A with vibration perception threshold and a negative correlation with neuropathy disability score. These findings suggest that even at the earliest stages of the glucose disturbances, Fetuin-A might play a key role in the development of the micro- and macrovascular complications, which are typical for people with T2DM.

This study had several limitations. The sample size was relatively small and study design was cross-sectional. Additional longitudinal clinical studies with larger number of patients are needed to fully clarify its role. Important strengths of this study are that all subjects were with obesity and that patients with glucose disturbances did not receive any glucose-lowering medications.

Conclusion

Serum level of Fetuin-A was significantly higher in patients with carbohydrate disturbances and correlated with the basic anthropometric and metabolic parameters, as well as with markers for micro- and macroangiopathy. Fetuin-A could be predictive for incidents of prediabetes and T2DM. Further studies are needed to fully evaluate the relationship of FetuinA with different vascular complications in patients with prediabetes and T2DM.

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