

Research paper

Serum fetuin-A levels are associated with serum triglycerides before and 6 months after bariatric surgery

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ABSTRACT

OBJECTIVE: The elucidation of the changes of fetuin-A in the context of bariatric surgery. **DESIGN:** Twenty obese patients (8 males, 12 females; body mass index = 42.5 ± 3.4 kg/m²) were studied at baseline and 6 months after bariatric surgery. **RESULTS:** Serum fetuin-A levels did not differ with regard to the presence of each individual component of the Metabolic Syndrome (MetS) at baseline, except for hypertriglyceridaemia [increased serum fetuin-A levels ($p=0.011$)]. Circulating fetuin-A was positively correlated with serum triglycerides (TG) ($r=0.461$, $p=0.047$) and negatively correlated with serum globulins ($r=-0.477$, $p=0.033$) and C-reactive protein (CRP) ($r=-0.604$, $p=0.010$), while it independently predicted TG at baseline. Circulating fetuin-A did not change during the 6 months either in the whole population or in the subgroups of patients who were positive for each individual component of MetS at baseline and negative for this component at 6 months of follow-up, except for hypertriglyceridaemia [reduction of serum fetuin-A levels ($p=0.046$)]. The subgroup of patients with a decrease in circulating fetuin-A during the 6 months was characterized by a smaller reduction of serum globulins ($p=0.003$) and CRP ($p=0.049$). The change in serum fetuin-A levels over the 6 months was positively correlated with the change in TG ($r=0.592$, $p=0.006$) and negatively correlated with the change in serum globulins ($r=-0.523$, $p=0.018$) and CRP ($r=-.494$, $p=0.037$). **CONCLUSIONS:** Circulating fetuin-A predicted serum triglycerides before as well as 6 months after bariatric surgery.

Key words: Metabolic syndrome, Obesity, Weight loss

INTRODUCTION

Fetuin-A, a plasma glycoprotein, is a negative acute phase reactant that is secreted predominantly by the

liver in adults.¹ Fetuin-A regulates calcium metabolism, being an important inhibitor of calcification in various tissues, including the vascular wall.² Another reported function of fetuin-A is the induction of insulin resistance through the inhibition of insulin receptor tyrosine kinase.³ Serum fetuin-A levels have been shown to be increased in patients with type 2 diabetes mellitus (T2DM) or metabolic syndrome (MetS), as well as in the presence of some individual components

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of MetS.⁴⁻⁶ However, there is an inconsistency in the results of the studies investigating the association of circulating fetuin-A with each individual component of MetS. Regarding the relationship of circulating fetuin-A with body weight status, although most of the studies have found a positive association between circulating fetuin-A and body mass index (BMI) and a reduction of serum fetuin-A levels after weight loss, some studies reported conflicting results.⁶⁻¹⁶

Bariatric surgery is a weight loss intervention achieved via an alteration not only of the passage of food through the gastrointestinal tract, but also of the secretion of gut hormones regulating appetite.¹⁷ Moreover, among weight loss interventions the magnitude of weight reduction after bariatric surgery is by far the greatest. Two studies that evaluated the changes in circulating fetuin-A after bariatric surgery found a decrease in serum fetuin-A levels, with one of the studies showing no change in circulating fetuin-A, though the exact metabolic role of fetuin-A in this context remains to be investigated.^{14,15,18} The relationship of the changes in circulating fetuin-A with the changes in body composition after bariatric surgery has not been previously investigated. Although body weight (BW) decreases progressively during the 12 months' period following bariatric surgery, loss of lean body mass (LBM) and reduction of basal metabolic rate (BMR) occur only up until completion of the first 6 months without any further decrease in the later period.^{19,20} Therefore, the first 6-month period following bariatric surgery represents the period of acute change in substrate utilization. The present study is a detailed analysis of body composition and a full assessment of glycaemic and lipoprotein parameters in obese patients undergoing bariatric surgery carried out to elucidate the relationship of the changes in circulating fetuin-A with the changes in metabolic parameters 6 months after bariatric surgery.

MATERIALS AND METHODS

Subjects

The study was conducted by the Laboratory of Physiology of the Medical School of Ioannina University in collaboration with the Obesity Clinic of the Diabetic Center and the Second Surgical Clinic of Tzaneio General Hospital. The study participants

were recruited from April 2012 to April 2013. Twenty obese subjects (8 men and 12 women) participated in the study. They were admitted to the surgical clinic to undergo a scheduled bariatric surgery. All patients were subjected to laparoscopic sleeve gastrectomy. Inclusion criteria for the study were BMI ≥ 40 kg/m² or BMI = 35-40 kg/m² with obesity-related comorbidities. Exclusion criteria were kidney disease, liver disease, gastrointestinal disease, neurological or psychiatric disorder, hypothyroidism, hyperthyroidism, malignancy, use of psychoactive substances and history of drug dependence. Lansoprazole 30 mg once daily was prescribed to all patients following surgery. There were 5 patients with T2DM and stable glycaemic control during follow-up who were taking the following antidiabetic medications: insulin (2), metformin (3), sulfonylureas (1), gliptins (1), thiazolidinediones (1), exenatide (1). Six patients had arterial hypertension and were taking the following antihypertensive medications: angiotensin II receptor antagonists (4), calcium channel blockers (1), diuretics (3), beta blockers (1). Five patients were under statin treatment. All patients provided written informed consent to participate in the study before the surgery. The study was approved by the Ethics Committee of the Tzaneio General Hospital.

Anthropometric measurements, body fat assessment and collection of venous blood samples after an overnight fast of at least 12 h were performed at baseline and 6 months after bariatric surgery. Serum samples were stored at -80 °C until analysis.

Body fat measurement

Body composition was assessed by Bioelectrical Impedance (BIA). The device used was the tetrapolar scale Tanita BC 418 MA (Tanita Corporation, Japan) which provided the BW and a complete body composition analysis. The Tanita BC 418 MA is a monofrequency BIA analyser which uses the frequency of 50 kHz and 8 electrodes integrated in the handles and the stepping platform for transmission of a weak electrical current through the body. The Tanita BC-418 MA can show separate body mass readings for each upper and lower limb and the trunk with the use of 8 polar electrodes. The Tanita formula takes into account gender, age, height, BW and distinguishes between "athlete" and "non-athlete". This instrument

can provide a complete body composition profile including Body Fat Percentage (BF%), Body Fat Mass (BFM), BMI, LBM, Estimated Muscle Mass, Total Body Water and BMR. All the measurements were performed in the morning before breakfast and after evacuation of the bladder. Patients were instructed to abstain from exercise, alcohol and caffeine during the day preceding the measurement of body composition. All the measurements were performed before bariatric surgery as well as 6 months after surgery.

Fetuin-A measurement

Serum fetuin-A levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (BioVendor Research and Diagnostic products, Brno, Czech Republic) with intra-assay CV 2.2-3.6 % and inter-assay CV 3.1-6.3 %.

Routine biochemical measurements and calculations

Fasting blood samples were analyzed for total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), glucose (Glc), insulin (Ins), glycated haemoglobin (HbA1c), uric acid, creatinine (Cre), total proteins (TPR), albumin, fibrinogen, C-reactive protein (CRP), thyroid-stimulating hormone (TSH), free thyroxine (FT₄) and triiodothyronine (T₃), using the standard procedures of the biochemistry laboratory of our Hospital. Homeostatic model assessment (HOMA)-index was calculated using the formula [fasting insulin (μU/mL) × fasting glucose (mg/dL)]/405. The quantitative insulin sensitivity check index (QUICKI) was calculated using the formula $1 / [\log \text{fasting insulin } (\mu\text{U/mL}) + \log \text{fasting glucose } (\text{mg/dL})]$. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation [LDL-C = TC - (HDL-C + TRG/5)]. Non-HDL-cholesterol (non-HDL-C) was calculated as TC - HDL-C. Serum levels of globulins were calculated as TPR - serum albumin.

Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics 23.0. The Kolmogorov-Smirnov test was used to verify the normality of the distributions of the parameters. All the studied parameters were normally distributed and were expressed as means ± SD. The paired t-test, independent t-test

and Pearson's correlation analysis were performed for normally distributed parameters. The Analysis of Variance (ANOVA) test was applied to determine whether circulating fetuin-A changed with the number of factors of MetS at baseline. Linear regression analysis was used to identify the independent predictors of TG at baseline. A two-tailed $p < 0.05$ was considered significant.

RESULTS

The characteristics of the patients at baseline and after 6 months following bariatric surgery are shown in Table 1. The reduction of BW ($24.9 \pm 9.1\%$) during the 6 months following bariatric surgery was accompanied by reduction of BFM, LBM and of both systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as by improvement of the lipid profile, as indicated by the decrease in TC, TG, LDL-C and the increase in HDL-C. Moreover, there was a reduction of insulin resistance following bariatric surgery, as indicated by the decrease in HOMA-index and the increase in QUICKI. TPR decreased during this period due to a reduction in serum globulins. The number of study participants who had MetS was 15 at baseline and 6 at 6 months of follow-up.

Comparisons at baseline

Serum fetuin-A levels did not differ between subjects with MetS and those without MetS ($p=0.622$) and did not change with the number of factors of MetS ($p=0.673$) at baseline. Serum fetuin-A levels did not differ with regard to the presence of each individual component of MetS at baseline, except for hypertriglyceridaemia, where increased serum fetuin-A levels were found in the presence of this component ($p=0.011$).

Correlation analysis at baseline

The relationship between serum fetuin-A levels and various parameters at baseline is shown in Table 2. Serum fetuin-A levels were positively correlated with TC, TG, LDL-C and non-HDL-C and negatively correlated with CRP, TPR and serum globulins at baseline. The association of circulating fetuin-A with globulins disappeared after adjustment for CRP. The relationship between circulating fetuin-A and lipid parameters did not change when a subgroup analysis was performed

Table 1. The characteristics of the patients (n = 20) at baseline and after 6 months of bariatric surgery

	Baseline	6 months	p (6 months vs baseline)
Body weight (Kg)	126.1 ± 21.1	94.8 ± 20.8	<0.001
BMI (Kg/m ²)	42.5 ± 3.4	32.0 ± 4.8	<0.001
BF% (%)	44.0 ± 6.9	34.7 ± 9.7	<0.001
BFM (Kg)	54.4 ± 10.6	34.7 ± 13.2	<0.001
LBM (Kg)	71.7 ± 16.9	60.1 ± 14.0	<0.001
WC (cm)	125.7 ± 14.2	104.5 ± 17.8	<0.001
SBP (mmHg)	138 ± 14	126 ± 11	<0.001
DBP (mmHg)	87 ± 11	77 ± 8	<0.001
TC (mg/dL)	220 ± 46	189 ± 33	0.010
TG (mg/dL)	132 ± 39	91 ± 29	<0.001
HDL-C (mg/dL)	40 ± 10	47 ± 15	0.045
LDL-C (mg/dL)	137 ± 34	126 ± 22	0.185
nonHDL-C (mg/dL)	180 ± 49	143 ± 22	0.003
Glc (mg/dL)	114 ± 41	98 ± 24	0.039
Ins (μU/mL)	19.3 ± 7.4	12.0 ± 4.7	<0.001
HbA1c (%)	6.5 ± 1.4	5.6 ± 0.9	0.001
HOMA-index	5.6 ± 3.3	3.0 ± 1.8	<0.001
QUICKI	0.305 ± 0.022	0.332 ± 0.024	<0.001
Uric acid (mg/dL)	6.5 ± 1.0	5.3 ± 1.1	<0.001
TPR (mg/dL)	7.3 ± 0.4	6.8 ± 0.5	0.002
Albumin (mg/dL)	4.3 ± 0.3	4.2 ± 0.3	0.392
Globulins (mg/dL)	2.9 ± 0.4	2.6 ± 0.4	0.001
CRP (mg/L)	13.3 ± 8.2	6.5 ± 4.3	<0.001
Fetuin-A (μg/mL)	268.1 ± 53.1	263.8 ± 68.4	0.808

Data are mean ± standard deviation for normally distributed variables. The p value refers to the comparison between baseline values and those 6 months after bariatric surgery.

Abbreviations: BFM: Body fat mass; BF%: Body fat percentage; BMI: Body Mass Index; CRP: C-reactive protein; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; FT₄: Free thyroxine; HbA1c: Glycated haemoglobin; HDL-C: High-density lipoprotein-cholesterol; HOMA-index: Homeostasis model assessment insulin resistance index; LBM: Lean body mass; LDL-C: Low-density lipoprotein-cholesterol; non-HDL-C: Non-HDL-cholesterol; QUICKI: Quantitative insulin sensitivity check index; Cre: Serum creatinine; Glc: Serum glucose levels; Ins: Serum insulin levels; TPR: Serum levels of total proteins; SBP: Systolic blood pressure; TSH: Thyroid-stimulating hormone; TC: Total cholesterol; TG: Triglycerides; T₃: Triiodothyronine; WC: Waist Circumference.

Table 2. The relationship between serum fetuin-A levels and various parameters at baseline

	r	p
Body weight	0.120	0.636
BMI	- 0.239	0.340
BF%	- 0.151	0.576
BFM	- 0.049	0.856
LBM	0.357	0.146
WC	0.268	0.267
SBP	- 0.334	0.150
DBP	- 0.203	0.391
TC	0.549	0.012
TG	0.461	0.047
HDL-C	- 0.036	0.881
LDL-C	0.540	0.012
nonHDL-C	0.524	0.018
HbA1c	0.395	0.105
HOMA-index	- 0.229	0.332
QUICKI	0.200	0.399
Uric acid	0.132	0.579
TPR	- 0.446	0.049
Albumin	0.181	0.445
Globulins	- 0.477	0.033
CRP	- 0.604	0.010

Abbreviations: BFM: Body fat mass; BF%: Body fat percentage; BMI: Body Mass Index; CRP: C-reactive protein; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; FT₄: Free thyroxine; HbA1c: Glycated haemoglobin; HDL-C: High-density lipoprotein-cholesterol; HOMA-index: Homeostasis model assessment insulin resistance index; LBM: Lean body mass; LDL-C: Low-density lipoprotein-cholesterol; non-HDL-C: Non-HDL-cholesterol; QUICKI: Quantitative insulin sensitivity check index; Glc: Serum glucose levels; Ins: Serum insulin levels; TPR: Serum levels of total proteins; SBP: Systolic blood pressure; TSH: Thyroid-stimulating hormone; TC: Total cholesterol; TG: Triglycerides; T₃: Triiodothyronine; WC: Waist Circumference.

excluding those taking lipid-lowering drugs. TG was positively correlated with WC (r=0.480, p=0.038) and tended to be correlated with Glc (r=0.408, p=0.074) at baseline, while there was no correlation with BW, BMI, BF%, Ins, HOMA-index and QUICKI. We performed multiple linear regression analysis to predict TG at baseline using as independent variables serum fetuin-

A levels ($\beta=0.455$, $p=0.042$), WC ($\beta 0.274$, $p=0.207$) and Glc ($\beta=0.348$, $p=0.108$). In this model (adjusted $R^2=0.348$, $p=0.024$) serum fetuin-A levels were the only variables that independently predicted TG.

Change in circulating fetuin-A after 6 months of follow-up

Serum fetuin-A levels did not change during the first 6 months following bariatric surgery in the whole population (Figure 1). Circulating fetuin-A did not change in the subgroup of patients who had MetS at baseline and no MetS at 6 months of follow-up ($p=0.194$), nor in the subgroup of patients whose number of components of MetS decreased during the period of 6 months ($p=0.506$). Serum fetuin-A levels did not change during this period in the subgroups of patients who were positive for each individual component of MetS at baseline and negative for this component at 6 months of follow-up, except for hypertriglyceridaemia, where there was a decrease in serum fetuin-A levels ($p=0.046$). A smaller reduction of both serum globulins ($p=0.003$) and CRP ($p=0.049$) was found in the subgroup of patients with a decrease in circulating fetuin-A at 6 months follow-up compared with those who did not have a decrease in circulating fetuin-A.

Correlation analysis during the 6 months of follow-up

The relationships between the change in serum

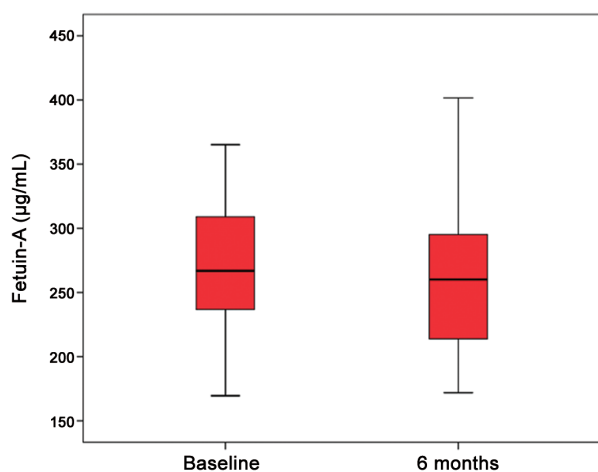


Figure 1. A box plot showing serum fetuin-A levels at baseline and 6 months following bariatric surgery. The difference in circulating fetuin-A between these time points was not significant.

fetuin-A levels and the changes in various parameters after 6 months' follow-up are shown in Table 3. The change in serum fetuin-A levels over this period was positively correlated with the change in TG and negatively correlated with the change in CRP, TPR and serum globulins, while there was a tendency for a positive relationship with the change in LBM and non-HDL-C. The relationship between the change in circulating fetuin-A and the change in TG persisted

Table 3. The relationship between the change in serum fetuin-A levels and the changes in various parameters 6 months after bariatric surgery.

	r	p
Change in body weight	0.288	0.246
Change in BMI	0.235	0.347
Change in BF%	0.114	0.654
Change in BFM	0.082	0.746
Change in LBM	0.411	0.090
Change in WC	0.350	0.168
Change in SBP	0.089	0.708
Change in DBP	0.033	0.889
Change in TC	0.307	0.188
Change in TG	0.592	0.006
Change in HDL-C	-0.174	0.463
Change in LDL-C	0.167	0.481
Change in nonHDL-C	0.411	0.072
Change in HbA1c	-0.071	0.766
Change in HOMA-index	-0.258	0.271
Change in QUICKI	0.418	0.075
Change in TPR	-0.495	0.026
Change in globulins	-0.523	0.018
Change in CRP	-0.494	0.037

Abbreviations: BFM: Body fat mass; BF%: Body fat percentage; BMI: Body Mass Index; CRP: C-reactive protein; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; FT₄: Free thyroxine; HbA1c: Glycated haemoglobin; HDL-C: High-density lipoprotein-cholesterol; HOMA-index: Homeostasis model assessment insulin resistance index; LBM: Lean body mass; LDL-C: Low-density lipoprotein-cholesterol; non-HDL-C: Non-HDL-cholesterol; QUICKI: Quantitative insulin sensitivity check index; Glc: Serum glucose levels; Ins: Serum insulin levels; TPR: Serum levels of total proteins; SBP: Systolic blood pressure; TSH: Thyroid-stimulating hormone; TC: Total cholesterol; TG: Triglycerides; T₃: Triiodothyronine; WC: Waist Circumference.

when a subgroup analysis was performed, excluding those taking lipid-lowering drugs. After performing multiple linear regression analysis, with the change in circulating fetuin-A as a dependent variable and the changes in TG, CRP, serum globulins and LBM as independent variables, only the change in TG was significantly correlated with the change in circulating fetuin-A (Table 4). The change in TG over 6 months after bariatric surgery was not correlated with changes in BW, BMI, WC, BF%, Glc, Ins, HOMA-index and QUICKI.

DISCUSSION

The present study found that although serum fetuin-A levels did not change 6 months after bariatric surgery, a reduction of circulating fetuin-A occurred more frequently in individuals with smaller reduction of globulins and CRP. Circulating fetuin-A independently predicted serum TG levels in a steady metabolic state, as well as 6 months after bariatric surgery.

We demonstrated no relationship of serum fetuin-A levels with BMI at baseline. The previously reported positive association of circulating fetuin-A with BMI referred to populations with a wide range of BMI, including not only obese patients, but also lean or overweight individuals.⁶⁻⁹ Thus, the fact that our study only evaluated subjects with BMI ≥ 35 kg/m² may have limited the potential for detection of significant associations between circulating fetuin-A and indices of obesity across the relatively narrow range of BMI of our study. Similarly, Himmetoglu et al found that although circulating fetuin-A was higher in morbidly obese patients compared with lean or overweight controls, it was not correlated with BMI in the subgroup of morbidly obese individuals.²¹ Moreover, the small

number and the heterogeneity of the participants of our study may have further contributed to the absence of any association between circulating fetuin-A and indices of obesity. The positive association of circulating fetuin-A with BMI has been reported in studies with at least an 8 times greater number of participants compared with our study. The previously reported positive association of circulating fetuin-A levels with BMI is possibly causal, as indicated by the fact that mice null for the fetuin-A gene had lower BW and were more resistant to weight gain after a high-fat diet compared with wild type mice.^{22,23}

The present study showed that serum fetuin-A levels did not change after 6 months of weight loss following bariatric surgery. This finding is consistent with the results of the study of Kahraman et al.¹⁸ Two other studies evaluated the changes in circulating fetuin-A at least 12 months after bariatric surgery.^{14,15} These studies found a decrease in serum fetuin-A levels at least 12 months after bariatric surgery.^{14,15} However, the abovementioned 3 studies did not perform an analysis of body composition. Interestingly, the change in circulating fetuin-A tended to be positively correlated with the change in LBM in our study, implying that a more negative nitrogen balance associated with a greater loss of LBM may downregulate the production of glycoprotein fetuin-A by the liver. Furthermore, the present study found that serum fetuin-A levels were negatively correlated with both serum globulins and CRP at baseline as well as 6 months after bariatric surgery. Weight loss is known to reduce CRP, possibly indicating a decrease in adipose tissue-induced inflammation.²⁴ In this context, the downregulation of positive acute phase reactants after weight reduction is expected to be accompanied by an upregulation of circulating fetuin-A, which, as mentioned above,

Table 4. Multiple linear regression analysis with the change in circulating fetuin-A as dependent variable

Dependent variable	Independent variables	Standardized β coefficient	p value for each independent variable	Adjusted R ² for the model	p value for the model
Change in fetuin-A	Change in TG	0.499	0.030	0.271	0.066
	Change in CRP	0.045	0.824		
	Change in globulins	- 0.271	0.212		
	Change in LBM	0.102	0.614		

Abbreviations: CRP: C-reactive protein; LBM: Lean body mass; TG: Triglycerides.

is a negative acute phase reactant.¹ Consistently, a smaller reduction of both serum globulins and CRP after bariatric surgery predicted a decrease in circulating fetuin-A in our study. The serum levels of globulins in our study possibly reflect the obesity-related low-grade inflammation, as indicated by the value of CRP. Hence, the property of fetuin-A as a negative acute phase reactant may have hindered the demonstration of a decrease in circulating fetuin-A after bariatric surgery in our study. This furnishes a plausible explanation for the absence of a decrease in circulating fetuin-A in the whole population of the present study. These considerations should be taken into account in the design of future studies investigating the metabolic role of fetuin-A, as well as in the interpretation of their results.

We found that among patients with BMI ≥ 35 kg/m² serum fetuin-A levels did not differ between those with MetS and those without MetS. The majority of studies have shown circulating fetuin-A to be upregulated in the presence of MetS among individuals with a wide range of BMI.^{6,9,25,26} However, the comparison between individuals with MetS and no MetS appears to be influenced by obesity.²⁷ Indeed, patients with BMI ≥ 35 kg/m² always fulfill the WC criteria of MetS, as demonstrated in our study.^{27,28} The latter individuals need to fulfill only 2 criteria of the remaining 4 to be diagnosed with MetS, lowering the threshold for the diagnosis of MetS in these patients and thus limiting the differences between the subjects with MetS and patients without MetS.²⁷ In this context, circulating fetuin-A may not have enough power to discriminate between MetS and non-MetS in patients with BMI ≥ 35 kg/m². Importantly, increased TG was the only component of MetS that was determined in our study by circulating fetuin-A at baseline, as well as 6 months after bariatric surgery. Indeed, increased TG appears to be the component of MetS with the most consistent association with serum fetuin-A levels in a steady metabolic state.^{6,29}

Our study demonstrated a positive relationship between serum levels of fetuin-A and TG at baseline as well as 6 months after bariatric surgery. Likewise, in the majority of studies serum TG levels have been reported to increase with increasing serum fetuin-A levels in a steady metabolic state.^{6,30-32} Furthermore, a fall in serum fetuin-A levels has been shown after

administration of TG-lowering medications, such as fenofibrate, n-3 polyunsaturated fatty acids and niacin.³³⁻³⁵ Kaushik et al reported that the niacin-induced change in circulating fetuin-A was positively correlated with the change in TG.³⁵ However, the relationship of the change in circulating fetuin-A with the change in TG during a weight loss intervention has not been previously investigated. The relationship between fetuin-A and TG is possibly causal, as indicated by the reported acceleration of exogenous fatty acid incorporation into cellular TG by fetuin-A.³⁶ Further studies are needed to confirm the presumed fetuin-A-induced upregulation of TG and elucidate the specific underlying mechanisms. Importantly, our study found for the first time that circulating fetuin-A was the only independent predictor of serum TG at baseline, implying a possible important role of fetuin-A in upregulating serum TG independently of all the traditional metabolic factors.

The current study found that circulating fetuin-A was positively correlated with non-HDL-C at baseline and the change in circulating fetuin-A tended to be positively correlated with the change in non-HDL-C after 6 months of follow-up. With regard to the relationship between serum levels of fetuin-A and LDL-C, a positive association was demonstrated only at baseline, but not during the 6 months of follow-up. The fact that a few patients were taking statins may have contributed to these negative results. A positive relationship of serum fetuin-A levels with both LDL-C and non-HDL-C has previously been shown in a steady metabolic state.^{6,30,31,37} However, the evaluation of the associations between the change in circulating fetuin-A and the changes in LDL-C and non-HDL-C during an intervention has not been performed before. The data of our study indicate the possible existence of a link between fetuin-A and the metabolism of ApoB-containing lipoproteins. This issue requires further investigation.

The results of our study should be interpreted in light of some limitations. Firstly, the small number of patients will have decreased the possibility of detecting significant changes in serum fetuin-A levels during follow-up, as well as significant associations of serum fetuin-A levels with metabolic parameters. This was true especially regarding subgroup analysis. Secondly, the study population was heterogeneous,

including patients with diabetes taking antidiabetic medications, individuals with arterial hypertension and patients taking lipid-lowering drugs, all these being situations that may have influenced serum fetuin-A levels. However, these relationships did not change when a subgroup analysis was performed excluding those taking lipid-lowering drugs. Thirdly, the BIA that was used to measure parameters of body composition, though an acceptable method, is not the gold standard. Moreover, we did not assess liver histology to determine if there was a relationship of fetuin-A with nonalcoholic liver disease. Fifthly, our study did not include a control group of healthy lean individuals to compare fetuin-A between the obese patients and the control group.

CONCLUSIONS

The current study found that serum fetuin-A levels independently predicted serum triglycerides before as well as during the first 6 months following bariatric surgery. Further well-designed studies are needed to confirm these results and investigate whether the relationship between fetuin-A and triglyceride metabolism is causal in humans.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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