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Original Article

Hepatokines Fetuin-A and Fetuin-B status in obese Saudi patient with diabetes mellitus type 2

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Abstract: The present study aims to investigate the association of the serum levels of Fetuin-A and Fetuin-B with type 2 diabetes mellitus (T2DM) in obese Saudi patients and explore the mechanism that links obesity and T2DM in Saudi patients. In this study, a total of 240 adult Saudis (116 men and 124 women) in the age group of 42.7±11.6 years were divided into three groups based on fasting blood glucose (FBG) levels: controls, T2DM and prediabetic. The levels of FBG, lipid profile and serum insulin were measured. Enzyme-linked immunosorbent assay (ELISA) was done to measure Fetuin-A, Fetuin-B and C-reactive protein (CRP). The results show that participants of the prediabetic and T2DM groups had significantly higher body mass index (BMI) values and elevated blood pressure (BP), FBG, total cholesterol (TC), triglyceride (TG), insulin, homeostatic model assessment-IR (HOMA-IR) and homeostatic model assessment-β (HOMA-β) as compared to the control group (P<0.001). The T2DM group participants exhibited significantly higher BMI, BP, FBG, TG, insulin, HOMA-IR and HOMA-β as compared to the prediabetic group participants (P<0.001). The serum levels of high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) were not significantly different among the three tested groups. The serum concentrations of CRP, Fetuin-A and Fetuin-B were slightly higher in T2DM patients as compared to the control group, but the difference failed to reach statistical significance (P>0.05). When results were segregated according to gender, FBG and HDL-C were significantly elevated (P=0.043 and P=0.002, respectively) in T2DM women (12.6±3.6 mmol/l and 1.0±0.3 mmol/l, respectively) compared to T2DM men (11.0±3.3 mmol/l and 0.86±0.2 mmol/l, respectively). However, the diastolic BP and waist-hip ratio (WHR) were significantly increased (P=0.010 and P=0.006, respectively) in T2DM men. The BMI and TC and all other measured parameters were similar between the two genders. Fetuin-A was significantly and positively associated with insulin levels (R=0.19, P=0.05), HOMA-IR (R=0.25, P=0.01) and TG (R=0.20, P=0.01) among overall participants of this study. The T2DM participants exhibited a significantly positive correlation with body weight. Fetuin-A was significantly and positively correlated with Fetuin-B in prediabetic participants, but this relation was not observed in the T2DM participants. Fetuin-B correlated inversely (P<005) with systolic BP (R=-0.20, P=0.01) and diastolic BP (R=-0.18, P=0.05). Interestingly, a strong inverse correlation was observed between Fetuin-B and TG in overall participants (R=-0.21, P=0.01) and specifically in T2DM women (R=-0.41, P=0.01). In conclusion, our study did not find a significant association of Fetuin-A or Fetuin-B levels in serum with T2DM. However, our results suggest that Fetuin-A may influence insulin resistance and serum Fetuin-B concentrations were inversely associated with TG in the general adult Saudi population.

Keywords: Fetuin-A, Fetuin-B, type 2 diabetes mellitus, Saudi Arabia

Introduction

Type 2 diabetes mellitus (T2DM) is a common type of diabetes among the top ten causes of death globally [1]. Diabetes had a worldwide prevalence of 10.5% (536.6 million) in adults aged 20-79 years old as of 2021, and it is expected to rise to 12.2% (783.2 million) in 2045 [1]. T2DM is strongly linked to visceral obesity and insulin resistance and has become a global health issue in recent decades, including Saudi Arabia [2]. This disorder can lead to microvascular and macrovascular complications and an increased risk of death. In addition, hepatic function could be impaired via T2DM. Several hepatic plasma proteins such as Fetuin-A, Fetuin-B and fibroblast growth factor-21 (FGF-21) may be involved in regulating insulin sensitivity, [3]. Fetuin-A, a hepatic secretory glycoprotein, has been identified as a sig-

nificant protein during fetal life. It is a natural tyrosine kinase inhibitor of the insulin receptor in the liver [3]. Furthermore, Fetuin-A is a critical component in the recovery phase of an acute inflammatory response, plays a role in insulin resistance, and is an independent predictor of type 2 diabetes. Furthermore, Fetuin-A acts as an essential novel mediator between diet and T2DM by inducing insulin resistance [4, 5]. Fetuin-B has been identified as a novel adipokine/hepatokine that significantly increases hepatic steatosis and mediates impaired insulin action and glucose intolerance [3]. Some studies suggest that high levels of circulating Fetuins are in line with insulin resistance and subclinical inflammation resulting in T2DM [4, 5].

Obesity is linked to a higher risk of developing T2DM. Although obesity is not the primary cause of T2DM, excessive carbohydrate consumption may result in an earlier onset of T2DM in genetically predisposed individuals. People genetically predisposed to develop T2DM are at high risk of becoming obese because of the inherent insulin resistance of their muscle and islet beta-cells, which promotes increased glucose and insulin release. Obesity is caused by increased hepatic glucose production and raised insulin levels due to insulin resistance [6]. The exact involvement of obesity in the association of the serum levels of Fetuin-A and Fetuin-B with T2DM in Saudi patients has not been fully clarified yet. Therefore, the present study is the first in Saudi Arabia to determine the association between serum Fetuin-A and Fetuin-B level in obese Saudi patients with T2DM. The present study may also help to explore the mechanism that links obesity and T2DM.

Materials and methods

A total of 240 adult Saudi (116 men and 124 women) individuals consented to participate in this observational cross-sectional study. The participants were collected from the Chair for Biomarkers of Chronic Diseases in Biochemistry Department, College of Science, King Saud University in Riyadh, Saudi Arabia. The participants were divided into three groups: Group-1 comprised of healthy control (37.2±12.4 years), Group-2 comprised of prediabetic participants (42.2±11.6 years) and Group-3 comprised of obese/T2DM patients (48.3±10.9 years). Before starting the study, we obtained ethical approval from the Institutional Review Board (IRB) of King Khalid University Hospital, Riyadh (IRB number E-20-5500). The study excluded non-Saudis and pregnant women.

Anthropometric assessment and data collection

Participants were asked to fill out questionnaires with demographic information and their past and present medical history. Anthropometric measurements with emphasis on clinical markers of adiposity were assessed. These included height (cm) and weight (kg) from which BMI was calculated [weight (kg)/height (m^2)]. Waist (cm) and hips (cm) circumferences were also measured, and their ratio was determined. Blood pressure (BP) (mmHg) was recorded twice after 30 minutes of rest using the conventional mercurial sphygmomanometer, and the average reading was recorded. Blood samples (approximately 5 ccs) obtained from the participants were transferred immediately to a non-heparinized tube for centrifugation and serum was obtained. On the same day as the collection, the serum was transferred to a pre-labeled tube, stored on ice, and delivered to the Chair for Biomarkers of Chronic Disease (CBCD) at King Saud University. Before analysis, the delivered fasting serum samples were stored in a -20°C freezer.

Biochemical assessment

The serum Fetuin-A and C-reactive protein (CRP) level were measured by sandwich enzyme immunoassay ELISA kit (R&D Systems Quantikine, Minneapolis, Minnesota, USA; Cat. #DFTA00, #DCRP00, #SCRP00, and #PDCRP00, respectively). The intra and inter-coefficient of variation for Fetuin-A was 4.3% and 7.3%, respectively, and the intra and inter-coefficient of variation for CRP was 5.5% and 6.5%, respectively. The serum Fetuin-B levels were measured by sandwich enzyme immunoassay ELISA kit (Biovendor, Karasek, Czech Republic; Cat. #RD191172200R). The intra and inter-coefficient of variation for Fetuin-B was 3.7% and 5.2%. The FBG, high-density lipoprotein-cholesterol (HDL-C), total cholesterol (TC) and triglycerides (TG) were measured by colorimetric methods using an automated chemical analyzer (Konelab, Thermo Scientific, Vantaa, Finland). The LDL-C was calculated using the Friedewald formula [LDL-C=TC-(HDL-C+(TG/5)] [7].

Table 1. Clinical characteristics of pre-diabetic, obese/T2DM and control subjects

Parameters	Control	Pre-Diabetics	Obese/T2DM	*P*-Value	Age & BMI adjusted *P*-value
N (M/F)	79 (39/40)	79 (41/38)	82 (36/46)		
Age (year)	37.2±12.4	42.2±11.6[A]	48.3±10.9[A,B]	<0.001	
Height (cm)	162.2±8.4	162.9±8.6	160.9±7.5	0.272	
Weight (kg)	61.1±10.8	83.8±19.5[A]	86.9±12.8[A]	<0.001	
BMI (kg/m^2)	22.7±3.5	31.6±6.9[A]	33.5±4.1[A,B]	<0.001	
WHR	0.87±0.10	0.91±0.1	0.94±0.1[A]	0.002	0.141
Systolic BP (mmHg)	113.3±10.9	121.4±13.1[A]	128.3±11.8[A,B]	<0.001	0.033
Diastolic BP (mmHg)	73.3±5.7	78.4±6.7[A]	81.7±6.9[A,B]	<0.001	0.002
Glucose (mmol/l)	4.6±0.6	6.1±0.5[A]	11.9±3.6[A,B]	<0.001	<0.001
Cholesterol (mmol/l)	4.5±0.9	4.9±1.1[A]	5.3±1.1[A]	<0.001	0.026
HDL Cholesterol (mmol/l)	1.1±0.3	0.98±0.3	0.96±0.3	0.055	0.645
LDL Cholesterol (mmol/l)	2.8±0.9	3.2±0.9[A]	3.3±0.9[A]	0.006	0.386
Triglycerides[#] (mmol/l)	1.2 (0.9-1.7)	1.6 (1.0-2.2)[A]	2.0 (1.5-2.9)[A,B]	<0.001	0.004
Pro-inflammatory markers					
Insulin (μU/ml)	3.3 (1.6-6.3)	3.8 (2.0-9.9)	8.7 (3.6-15.5)[A]	0.001	0.215
HOMA-IR (μU/ml)	0.73 (0.14-3.73)	1.02 (0.20-11.8)[A]	4.10 (0.12-26.7)[A,B]	<0.001	<0.001
HOMA-β	65.5 (28.1-97.9)	32.2 (17.4-91.0)	21.1 (7.1-38.8)[A,B]	<0.001	0.001
CRP (pg/ml)	4.6 (1.9-10.1)	5.4 (2.2-13.5)	10.7 (2.8-24.1)	0.056	0.476
Fetuin-A (pg/ml)	3.86±1.9	3.96±1.8	4.19±1.8	0.535	0.439
Fetuin-B (pg/ml)	0.39 (0.34-1.72)	0.37 (0.35-2.19)	0.36 (0.11-0.80)	0.088	0.123

Note: Data presented as mean ± SD for continuous normal variables and medians (25th percentile, 75th percentile) for continuous non-normal variables. *P*-value is significant at 0.05 & 0.01 level. Superscripts A and B represent significant respectively for control and pre-diabetics data presented as coefficient (R). [#]denotes not normal.

The fasting serum insulin level was measured by using the chemiluminescence immunoassay Kit (LIAISON Insulin ([REF] 310360).

Statistical analysis

Data were analyzed using SPSS (version 22 Chicago, IL, USA). Continuous data were presented as mean ± standard deviation (SD) for normal variables and non-Gaussian variables were presented in median (1st and 3rd) percentiles. Categorical data were presented as frequencies and percentages (%). Besides, all continuous variables were checked for normality using the Kolmogorov-Smirnov test. Non-Gaussian variables were log-transformed before parametric analysis. An independent t-test and Manan-Whitney U tests were used to compare mean and median difference between gender for control, prediabetic and diabetic groups. One-way analysis of variance (ANOVA) and Kruskal-Wallis H test were performed for mean and median difference between groups (control, prediabetic and diabetic) and further Bonferroni test was performed for post-hoc analysis. Pearson's and Spearman's correlation analysis was performed for fetuin-A and fetuin-B with anthropometrics, biochemical and pro-inflammatory markers. *P*-value <0.05 was considered statistically significant.

Result

The mean age for all 240 participants (116 men and 124 women) was 48.3±11.6 years.

Table 1 summarizes the clinical characteristics of the participants from all three groups. The result showed a significant age difference, so after adjustment for age and BMI, the *p*-value was recalculated. The BMI of the obese/T2DM group was the highest (33.5±4.1 kg/m^2) followed by the prediabetic group (31.6±6.9 kg/m^2) and it was the least for the control group (22.7±3.5 kg/m^2). The obese/T2DM subjects had significantly raised BP as compared to prediabetic subjects. Whereas the prediabetic subjects were significantly hypertensive as compared to controls. The fasting blood glucose was significantly raised in participants of the obese/T2DM group (11.9±3.6 mmol/l) as compared to prediabetics (6.1±0.5 mmol/l) and controls (4.6±0.6 mmol/l). Insulin levels were higher in the obese/T2DM group (8.7

Table 2. Clinical characteristics of pre-diabetic, obese/T2DM and control and all with respect to gender

Parameters	Control			Pre-Diabetics			Obese/Type 2DM			All		
	Men	Women	*P*-Value	Men	Women	*P*-Value	Men	Women	*P*-Value	Men	Women	*P*-Value
N (M/F)	39	40		41	38		36	46		116	124	
Age (year)	36.0±12.1	38.4±12.8	0.39	43.7±11.9	40.5±11.2	0.22	48.1±13.8	48.5±8.1	0.87	42.3±13.4	42.8±11.5	0.83
Height (cm)	167.6±6.6	156.7±6.2	<0.001	167.7±8.2	157.8±5.3	<0.001	166.1±6.1	156.8±5.9	<0.001	167.1±7.1	157.1±5.8	<0.01
Weight (Kg)	61.9±10.3	60.3±11.5	0.52	87.7±19.2	79.5±19.1	0.06	91.5±13.7	83.3±10.8	0.003	80.2±19.8	74.9±17.2	0.030
BMI (kg/m^2)	21.9±3.1	23.5±3.7	0.04	31.2±6.0	32.0±7.7	0.59	33.2±4.5	33.8±3.6	0.48	28.7±6.8	29.9±6.9	0.16
WHR	0.92±0.10	0.84±0.10	<0.001	0.96±0.1	0.86±0.1	<0.001	0.97±0.1	0.91±0.1	0.006	0.95±0.11	0.87±0.10	<0.01
Systolic BP (mmHg)	113.9±7.4	112.8±13.6	0.69	124.1±13.3	118.4±12.3	0.06	131.0±11.3	126.0±11.8	0.06	123.1±12.9	119.4±13.6	0.04
Diastolic BP (mmHg)	74.3±6.3	72.4±4.9	0.17	80.0±6.1	76.6±6.8	0.024	83.9±6.4	79.9±6.9	0.010	79.4±7.3	76.5±6.9	0.002
Glucose (mmol/l)	4.6±0.6	4.6±0.5	0.63	6.1±0.5	6.1±0.5	0.92	11.0±3.3	12.6±3.6	0.043	7.1±3.3	8.0±4.2	0.07
Cholesterol (mmol/l)	4.3±0.8	4.7±1.1	0.12	5.0±1.2	4.9±0.9	0.68	5.3±1.0	5.4±1.3	0.64	4.9±1.1	5.0±1.2	0.31
HDL Cholesterol (mmol/l)	0.92±0.2	1.2±0.3	<0.001	0.89±0.3	1.1±0.3	0.004	0.86±0.2	1.0±0.3	0.002	0.89±0.2	1.10±0.3	<0.001
LDL Cholesterol (mmol/l)	2.7±0.8	2.8±0.9	0.41	3.1±1.0	3.2±0.9	0.85	3.3±0.8	3.3±0.9	0.95	3.0±0.9	3.1±1.0	0.55
Triglycerides# (mmol/l)	1.2 (0.9-1.7)	1.1 (0.8-1.6)	0.29	2.1 (1.2-2.7)	1.4 (0.9-1.8)	0.002	2.0 (1.5-2.9)	1.9 (1.4-2.9)	0.24	1.8 (1.1-2.4)	1.4 (0.9-2.0)	0.008
Pro-inflammatory markers												
Insulin (μU/ml)	3.3 (1.5-5.2)	3.5 (2.1-6.4)	0.62	6.2 (2.8-14.9)	3.4 (1.8-4.4)	0.06	8.0 (2.4-31.9)	9.1 (3.6-12.7)	0.67	4.7 (1.7-14.9)	4.1 (2.9-9.8)	0.44
HOMA-IR (μU/ml)	0.70 (0.14-3.73)	0.73 (0.16-2.15)	0.93	3.46 (0.33-11.8)	0.98 (0.2-10.3)	0.040	4.1 (0.12-26.7)	4.10 (0.33-13.2)	0.56	1.6 (0.12-26.7)	1.4 (0.16-13.2)	0.33
HOMA-β	61.1 (25.1-106.3)	71.9 (44.6-97.9)	0.64	48.6 (17.4-126.3)	24.9 (15.4-39.5)	0.055	19.3 (7.4-96.1)	21.1 (6.6-30.7)	0.32	42.7 (15.3-117.3)	27.3 (14.1-63.3)	0.084
CRP (pg/ml)	2.6 (1.1-8.9)	5.5 (2.3-10.3)	0.23	4.5 (2.2-10.3)	6.0 (3.3-13.6)	0.45	4.9 (2.8-24.7)	12.2 (2.5-23.6)	0.66	4.2 (2.1-10.3)	6.6 (2.4-15.1)	0.08
Fetuin-A (pg/ml)	4.29±2.3	3.42±1.5	0.06	4.12±1.6	3.79±1.9	0.42	4.34±1.9	4.10±1.8	0.51	4.24±1.9	3.78±1.7	0.49
Fetuin-B (ng/ml)	0.39 (0.14-2.23)	0.39 (0.35-1.58)	0.71	0.37 (0.33-2.73)	0.36 (0.35-1.95)	0.67	0.35 (0.12-0.42)	0.36 (0.09-1.19)	0.67	0.38 (0.1-1.9)	0.37 (0.2-1.4)	0.81

Note: Data presented as mean ± SD for continuous normal variables and medians (25th percentile, 75th percentile) for continuous non-normal variables. *P*-value is significant at 0.05 & 0.01 level. Data presented as coefficient (R); #denotes not normal.

(3.6-15.5) μU/ml) as compared to the control group (3.8 (2.0-9.9) μU/ml), while there was no difference in levels of insulin in prediabetics when compared to controls (3.3 (1.6-6.3) μU/ml). TC was significantly higher in prediabetics (4.9±1.1 mmol/l) as compared to the control group (4.5±0.9 mmol/l). The LDL-C was higher in the obese/T2DM group (3.3±0.9 mmol/l) and prediabetic group (3.2±0.9 mmol/l) as compared to the control group (2.8±0.9 mmol/l); also, the levels of TG differed significantly in the obese/T2DM group (2.0 (1.5-2.9) mmol/l) and prediabetic group (1.6 (1.0-2.2) mmol/l) when compared to the control group (1.2 (0.9-1.7) mmol/l). Serum levels of CRP, Fetuin-A, and Fetuin-B were not significantly different between the study groups (diabetes and prediabetes) and the control group. Finally, the HOMA-IR in obese/T2DM was highest (4.10 (0.12-26.7) μU/ml) followed by prediabetic (1.02 (0.20-11.8) μU/ml) and it was lowest for the controls (0.73 (0.14-3.73) μU/ml). HOMA-β was highest in obese/T2DM (21.1 (7.1-38.8)) compared to prediabetic (32.2 (17.4-91.0)) and the control (65.5 (28.1-97.9)).

Table 2 summarizes the clinical characteristics of the three groups with respect to gender. The result showed no significant difference in serum CRP, Fetuin-A, and Fetuin-B between the study groups (men and women) in obese/T2DM groups compared to the control group. Overall, the levels of TG were found to be significantly higher (P=0.008) in men than in women, and this gender bias for TG was observed to be more significant (P=0.002) in the prediabetic men (2.1 (1.2-2.7) mmol/l) than women (1.4 (0.9-1.8) mmol/l), but it failed to reach significance among participants of obese/T2DM group and control group. Fasting blood glucose was significantly (P=0.043) elevated in obese women with T2DM (12.6±3.6 mmol/l) than men (11.0±3.3 mmol/l) of this group; other groups showed no gender difference in blood glucose level. Overall the men were significantly (P<0.01) taller than the women. Similarly, the waist-hip ratio (WHR) recorded for all men was significantly (P<0.01) higher than women who participated in this study. However, the levels of HDL-C were higher in women (1.10±0.3 mmol/l) than in men (0.89±0.2 mmol/l) overall groups. Overall the mean body weight was significantly (P=0.030) larger for the men (80.2± 19.8 Kg) than women (74.9±17.2 Kg), and as expected, it was significantly (P=0.003) higher among the obese men with T2DM (91.5±13.7 Kg) when compared to obese women (83.3± 10.8 Kg) with T2DM. Diastolic BP was comparable between men and women of the control group but was significantly higher among prediabetic men and the obese men with T2DM than in the case of women of these groups.

Table 3 summarizes the correlation analysis for Fetuin-A (pg/ml) with other parameters. Among all participants of this study, Fetuin-A was found positively associated with TG (P= 0.01, R=0.20), insulin levels (P=0.05, R=0.19) and HOMA-IR (P<0.01, R=0.25). Irrespective of gender, Fetuin-A was significantly and positively correlated to weight among the obese/T2DM participants (P=0.05, R=0.22). Also, Fetuin-A was significantly and positively correlated with Fetuin-B (P=0.05, R=0.24) in prediabetic participants. Fetuin-A was significantly and positively correlated with TG (P= 0.01, R=0.30) and negatively correlated with LDL-C (P=0.05, R= -0.23) in the control group. In women prediabetic participants, the Fetuin-A was significantly and positively correlated with Fetuin-B (P=0.05, R=0.35) and significantly but negatively correlated with diastolic BP (P=0.05, R= -0.36). In men's obese/T2DM group, Fetuin-A was significantly and positively correlated with HDL-C (P=0.05, R=0.34); in men's control group, Fetuin-A was significantly and positively correlated with TG (P=0.05, R=0.35) and negatively correlated with height and LDL-C (P=0.05, R=-0.38 and P=0.01, R=-0.43 respectively). Finally, in men prediabetic participants, the Fetuin-A was significantly and negatively correlated with height (P=0.05, R=-0.39).

Table 4 summarizes the correlation analysis for Fetuin-B (pg/ml) with other parameters. Among all participants of this study, Fetuin B was found significantly and negatively associated with systolic BP, diastolic BP and TG (P=0.01, R=-0.20 and P=0.05, R=-0.18 and P=0.01, R=-0.21 respectively). Irrespective of gender, in prediabetic participants, the Fetuin-B was found significantly and positively associated with Fetuin-A (P=0.05, R=0.24); also, the Fetuin-B was found significantly and negatively associated with glucose (P=0.05, R=-0.27). Among the women prediabetic participants, Fetuin-B was found to be significantly and positively associated with HDL-C (P=0.05, R=0.37)

Table 3. Correlation analysis for Fetuin-A (pg/ml) with other parameters

Parameters	All	All			Men			women		
		Control	Pre-Diabetics	Obese/T2DM	Control	Pre-Diabetics	Obese/T2DM	Control	Pre-Diabetics	Obese/T2DM
N (M/F)	230	79	79	82	39	41	36	40	38	46
Age (year)	0.06	-0.04	0.05	0.12	-0.03	0.17	0.12	0.01	-0.10	0.13
Height (cm)	-0.03	-0.08	-0.12	0.15	-0.38*	-0.39*	0.23	-0.16	0.03	0.05
Weight (Kg)	0.08	0.00	0.00	0.22*	-0.22	-0.06	0.29	0.28	0.01	0.13
BMI (kg/m^2)	0.09	0.06	0.04	0.15	-0.02	0.14	0.19	0.29	-0.03	0.11
WHR	0.10	0.05	0.08	0.12	-0.16	0.17	0.13	0.10	-0.09	0.08
Systolic BP (mmHg)	0.08	0.07	0.04	0.01	0.16	0.20	-0.09	0.01	-0.17	0.07
Diastolic BP (mmHg)	0.03	0.05	-0.07	-0.01	0.02	0.21	0.10	0.01	-0.36*	-0.15
Glucose (mmol/l)	0.08	0.16	-0.17	0.03	0.12	-0.13	0.00	0.22	-0.21	0.09
Cholesterol (mmol/l)	-0.03	-0.16	-0.05	0.05	-0.30	-0.02	0.04	0.04	-0.10	0.06
HDL Cholesterol (mmol/l)	-0.03	-0.16	0.01	0.09	-0.14	-0.14	0.34*	0.03	0.19	-0.01
LDL Cholesterol (mmol/l)	-0.11	-0.23*	-0.11	-0.05	-0.43**	-0.06	-0.15	-0.02	-0.17	0.02
Triglycerides# (mmol/l)	0.20**	0.30**	0.12	0.15	0.35*	0.17	0.11	0.20	0.00	0.19
Pro-inflammatory markers										
Insulin (μU/ml)	0.19*	0.08	0.05	0.19	0.05	0.04	0.33	0.26	0.02	0.00
HOMA-IR (μU/ml)	0.25**	0.02	0.04	0.17	0.08	0.04	0.32	-0.09	0.01	-0.05
HOMA-β	0.01	0.08	0.10	0.18	-0.02	0.10	0.30	0.41	0.08	0.04
CRP (pg/ml)	-0.03	-0.11	-0.08	0.11	-0.10	-0.07	-0.07	-0.09	-0.10	0.14
Fetuin-B (pg/ml)	0.12	0.13	0.24*	-0.14	0.09	0.12	0.01	0.18	0.35*	-0.23

Note: Data presented as mean ± SD for continuous normal variables and medians (25th percentile, 75th percentile) for continuous non-normal variables. *P*-value is significant at 0.05 & 0.01 level. Data presented as coefficient (R); #denotes not normal; *denotes significance at 0.05 level; **denotes significance at 0.01 level.

Table 4. Correlation analysis for Fetuin-B (pg/ml) with other parameters

Parameters	All	All			Men			women		
		Control	Pre-Diabetics	Obese/T2DM	Control	Pre-Diabetics	Obese/T2DM	Control	Pre-Diabetics	Obese/T2DM
N (M/F)	230	79	79	82	39	41	36	40	38	46
Age (year)	-0.05	0.08	-0.06	-0.04	0.13	-0.07	0.19	0.05	-0.07	-0.26
Height (cm)	-0.06	-0.09	-0.16	0.02	-0.11	-0.35*	0.24	-0.35	-0.01	-0.01
Weight (Kg)	-0.05	0.19	-0.08	-0.08	0.24	-0.31	-0.01	0.13	0.16	-0.09
BMI (kg/m^2)	-0.04	0.22	0.01	-0.11	0.35	-0.13	-0.13	0.15	0.16	-0.10
WHR	0.04	0.02	0.10	0.07	0.03	0.18	-0.17	0.00	-0.11	0.22
Systolic BP (mmHg)	-0.20**	-0.12	-0.14	-0.21	-0.04	-0.21	-0.17	-0.18	-0.06	-0.22
Diastolic BP (mmHg)	-0.18*	-0.09	-0.19	-0.14	-0.25	-0.29	-0.26	0.12	-0.10	-0.06
Glucose (mmol/l)	-0.12	0.15	-0.27*	0.04	0.07	-0.27	0.19	0.26	-0.29	-0.06
Cholesterol (mmol/l)	-0.05	-0.08	-0.05	0.05	-0.29	0.00	0.19	0.06	-0.15	-0.01
HDL Cholesterol (mmol/l)	0.10	-0.04	0.10	0.19	-0.15	-0.08	0.18	0.05	0.37*	0.18
LDL Cholesterol (mmol/l)	-0.02	-0.02	0.00	0.01	-0.20	0.18	0.02	0.12	-0.22	0.01
Triglycerides# (mmol/l)	-0.21**	-0.12	-0.20	-0.19	-0.09	-0.34*	0.23	-0.17	-0.14	-0.41**
Pro-inflammatory markers										
Insulin (μU/ml)	0.19*	0.08	0.05	0.19	0.05	0.04	0.33	0.26	0.02	0.00
HOMA-IR (μU/ml)	0.25**	0.02	0.04	0.17	0.08	0.04	0.32	-0.09	0.01	-0.05
HOMA-β	0.01	0.08	0.10	0.18	-0.02	0.10	0.30	0.41	0.08	0.04
CRP (pg/ml)	-0.03	-0.11	-0.08	0.11	-0.10	-0.07	-0.07	-0.09	-0.10	0.14
Fetuin-B (pg/ml)	0.12	0.13	0.24*	-0.14	0.09	0.12	0.01	0.18	0.35*	-0.23

Note: Data presented as mean ± SD for continuous normal variables and medians (25th percentile, 75th percentile) for continuous non-normal variables. *P*-value is significant at 0.05 & 0.01 level. Data presented as coefficient (R); #denotes not normal; *denotes significance at 0.05 level; **denotes significance at 0.01 level.

and Fetuin-A (P=0.05, R=0.35). In women of control group, Fetuin-B was found significantly and positively associated with CRP (P=0.05, R=0.51). The obese women/T2DM participants showed that, Fetuin-B was found significantly and negatively associated with TG (P=0.01, R=-0.41). Finally, among the men of prediabetic group, Fetuin-B was found significantly and negatively associated with height, TG, and CRP (P=0.05, R=-0.35 and P=0.05, R=-0.34 and P=0.05, R=-0.44 respectively).

Discussion

T2DM, robustly linked with obesity and insulin resistance, has become a global health issue in recent decades [1]. This disease adversely affects various vital organs and results in reduced life expectancy. The liver is one such organ that gets impaired because of T2DM. Fetuin-A and Fetuin-B are hepatic plasma proteins that have been implicated in T2DM pathogenesis since they may impair insulin secretions from β-cells, induce lower insulin sensitivity and causes subclinical inflammation [3]. So far as we know, the relationship of T2DM with Fetuin-A and Fetuin-B has been studied in several populations, but it has not been studied in Saudi Arabia yet. Thus, our present study is the first to investigate the association of serum Fetuin-A and Fetuin-B levels with T2DM in adult obese patients of Saudi ethnicity.

Based on glucose tolerance status, individuals with serum levels of FPG of ≥126 mg/dl (6.99 mmol/l) are classified as diabetic and those with FPG of 100-125 mg/dl (5.54 mmol/l-6.93 mmol/l) are classified as having prediabetes in the Saudi population [8, 9]. We followed these diagnostic criteria and stratified the study participants into three groups: non-diabetic (control), prediabetic, T2DM. Except for the participants of the control group, all other participants (prediabetic and T2DM) were obese (BMI>30).

Elevated serum levels of Fetuin-A were reported to be associated with T2DM and insulin resistance by studies done in Chinese [10] as well as in several other populations [11-13]. In concordance with some previous studies [14, 15], the difference in serum Fetuin-A levels between the three studied groups was insignificant in our result. Nevertheless, it is noteworthy that after simple regression analyses, serum Fetuin-A levels were in a significant direct correlation with HOMA-IR and insulin in overall participants of the current study. Thus, our results suggest that Fetuin-A may influence insulin resistance in the general adult Saudi population independent of obesity and glucose tolerance status. Our results reinforce previous studies which reported no differences in Fetuin-A levels between the T2DM and non-diabetic groups but demonstrated an independent impact of Fetuin-A on insulin resistance in non-diabetic subjects [14, 16]. Fetuin-A has been linked with insulin sensitivity in individuals who are free of diabetes or any other chronic disease [15, 17-20]. Thus Fetuin-A may play a physiological role in regulating insulin signaling. T2DM is characterized by insulin insensitivity due to insulin resistance, declining insulin production, and eventual pancreatic β-cell failure [21]. The T2DM and prediabetic groups in our study exhibited HOMA-IR values that were much higher than those for the control group, indicating that insulin resistance was prevalent among them. This agrees with HOMA-IR results determined previously in T2DM Saudi patients [22].

The lack of difference in Fetuin-A levels between the three studied groups in the present study could be because the measured concentrations of Fetuin-A may have been masked in T2DM and prediabetic groups due to glycation of Fetuin-A in these participants. Further, the medications taken by prediabetic or T2DM participants could have altered the levels of Fetuin-A in serum. Although elevated glucose concentration has been demonstrated to increase the Fetuin-A gene expression, other factors can influence the synthesis and breakdown of this glycoprotein [23]. For example, pro-inflammatory cytokines can reduce the expression of the Fetuin-A gene [24]. Obesity is an important feature of metabolic syndrome and it predisposes individuals to a pro-inflammatory state via increased inflammatory mediators IL-6 and TNF-α [25, 26]. This is confirmed by several studies done on obese T2DM patients in Saudi Arabia [27], America [28, 29], India [30, 31] and Pakistani [32]. One study found high Fetuin-A levels in subcutaneous adipose tissues of obese diabetics not in circulation, suggesting that adipose tissues act as a sponge for Fetuin-A storage by temporary protection against excessive levels in circulation [33].

Cardiovascular risk factors like obesity, hyperglycaemia, hypertriglyceridemia, abnormal LDL-

C and HDL-C levels, and hypertension collectively represent metabolic syndrome (MetS). In the Arabian Gulf region, the prevalence of MetS varies from 20.7% to 37.2% in males and 32.1% to 42.7% in females. In Saudi Arabia, the age-adjusted prevalence of MetS in males and females was reported to be 37.2% and 42%, respectively [34]. MetS were found in the participants of the T2DM group of the present research. Obesity, hyperglycemia, hypertension, and hypertriglyceridemia were the commonest component of the syndrome in all T2DM patients. However, except for hyperglycemia, combinations of all other components of MetS were significantly more pronounced among T2DM men participants. The current research detected a strong link of Fetuin-A with various features of the MetS. Such as blood pressure, waist circumference, and HDL-C. This finding is compatible with previous studies that discuss the association of Fetuin-A with MetS manifestations in general [35-37]. However, the studies investigating the association of circulating Fetuin-A with each component of MetS show variable results. For example, most of the studies have agreed that there exists a direct association between circulating Fetuin-A and body mass index (BMI), yet some studies reported conflicting results [38]. Among Saudi patients, we found body weight to be correlated positively with Fetuin-A levels. Thus, we believe that the measurement of plasma Fetuin-A may be particularly important for the evaluation of the individual risk of T2DM. The role of Fetuin-A in the pathophysiology of MetS and low-grade inflammation has been reported [17] and our results are in agreement.

The positive correlation of Fetuin-A levels with TG levels in the participants of the control group in the present study agrees with a study by Verras et al. [38] and suggests that circulating Fetuin-A can independently predict serum TG levels in a steady metabolic state. The correlation of Fetuin-A with HDL-C was significant, particularly in T2DM males. Among T2DM females, HDL-C levels did not correlate with Fetuin-A significantly. Fetuin-A may alter the lipid profile, which directly or indirectly affects the tyrosine kinase activity at the insulin receptor. Our study results indicate that Fetuin-A is likely to be a novel link between obesity and its comorbidities. This may also explain the underlying mechanism for altered lipid profile in T2DM and its relation to insulin resistance. Studies done in Saudi Arabia have also shown that altered lipid profile in T2DM due to alterations in metabolism is linked to insulin resistance. It was observed that there was a significant increase in cholesterol and TG and a decrease in HDL without any significant alteration in LDL-C in Saudi patients with T2DM [8, 39]. Studies done in the Chinese population also found T2DM patients to have significantly higher TC and LDL than the control group [35].

Qu et al. were the pioneers to investigate the link between Fetuin-B and T2DM patients. Their study revealed that Fetuin-B was positively correlated with glucose tolerance [35]. Later, several other studies have also found a link between Fetuin-B and T2DM. Li et al. discovered that subjects with T2DM had significantly higher serum Fetuin-B than the non-diabetic subjects. However, in their study, the positive association of serum Fetuin-B with T2DM became non-significant with further adjustment for metabolic/insulin resistance syndrome [40].

Fetuin-B plays an important role in regulating oozyte function and fertility [41], but no receptor-mediated signaling of Fetuin-B to regulate glucose metabolism is known. The Fetuin-B levels were similar in our research's three study groups, and the association of Fetuin-B with insulin levels was non-significant. Our results support the observation of Meex et al. [42] that Fetuin-B may be involved in the regulation of glucose effectiveness, which refers to the ability of glucose to promote its own disposal independent of insulin, in animal models [43, 44]. Although Fetuin-B caused glucose intolerance in mice, it did not impair insulin signaling after glucose administration. Further, it did not reduce insulin sensitivity during hyperinsulinemic-euglycemic clamping in mice. So it appears that Fetuin-A and Fetuin-B regulate glucose homeostasis by dissimilar mechanisms.

An interesting observation of our research was that Fetuin-B was significantly and positively correlated with Fetuin-A in the prediabetic women participants. Denecke et al. found that although Fetuin-B shares some similarities with Fetuin-A, Fetuin-B's function was not identical to that of Fetuin-A. Whereas a causal role of Fetuin-A in insulin resistance is well established, the involvement of Fetuin-B in the occurrence of insulin resistance has rarely been

studied [45]. Peter et al. found that the Fetuin-A and Fetuin-B might regulate glucose metabolism in slightly different ways, with Fetuin-A modulating insulin signaling and Fetuin-B affecting glucose effectiveness [46].

A potential lipid-regulating role of Fetuin-B was seen in our study since we found that Fetuin-B was significantly and negatively associated with TG in overall participants and specifically in T2DM women and prediabetic men. A significant direct association of Fetuin-B with HDL cholesterol was observed in prediabetic women. Further, Fetuin-B was found to be inversely associated with BP in overall participants. This finding supports the study, which stated that increased levels of Fetuin-B may play a role in vascular endothelial protection [47].

This study has some limitations that should be considered. First, the lack of significance in the concentration of our interest hepatokines might be due to the small sample number that contributed to the failure of some comparisons to reach statistical significance. Second, we did not have the onset of T2DM data in this study. Third, the gene polymorphism of these proteins in Saudi T2DM subjects hasn't been explored; it's important to mention the cross-sectional nature, making the interpretation of the results limited. Fourth, further studies with a larger sample size that include T2DM patients with other chronic complications and type 1 diabetes (T1D) should be performed to compare the action of Fetuin-A and Fetuin-B. Also, measurement of the Hb1AC is highly recommended. Finally, study how we can use Fetuin-A and Fetuin-B to treat T2DM needs to be conducted.

Conclusion

This study did not find Fetuin-A or Fetuin-B levels in serum to be associated with T2DM. However, our results suggest that Fetuin-A may influence insulin resistance in the general adult Saudi population. We also found that serum Fetuin-A independently predicted serum TG levels in a steady metabolic state. Our results support the hypothesis that Fetuin-A may be involved in the pathogenesis of insulin resistance. This may contribute to future T2DM and metabolic syndrome development among Saudi adults. Serum Fetuin-B concentrations were inversely associated with TG in the general adult Saudi population thus Fetuin-B may play a role in vascular endothelial protection.

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Disclosure of conflict of interest

None.

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