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Effects of Inflammatory Biomarkers (Fetuin-A and High Sensitivity C-reactive Protein) on Glycemic Control in Type 2 Diabetic Women

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ABSTRACT

OBJECTIVE Inflammation plays an essential role in the development of insulin resistance and type 2 diabetes. The objective of this study was to evaluate the effects of inflammatory markers (hs-CRP and fetuin-A) on glycemic control in Iraqi women patients with type 2 diabetes, and to examine the correlation of these markers with indices of glycemic control.

METHODS This case-control study included 45 Iraqi type 2 diabetic female patients and 44 non-diabetic Iraqi female patients matched for age and sex as control subjects. For both patients and controls hs-CRP and fetuin-A were measured using ELISA, HbA1c by the turbidimetric immunoassay, FBG and lipid profile measures using the spectrophotometer method.

RESULTS High levels of both fetuin-A and hs-CRP were observed in diabetic patients compared to the healthy controls. hs-CRP was significantly higher in the diabetic group 3.1 ± 0.59 mg/dL than the control 1.22 ± 0.66 mg/dL and was statistically significantly correlated with the marker of glycemic control ($p < 0.001$). The serum level of fetuin-A in the diabetic group (768.7 ± 173.03 µg/mL) was also significantly higher than that of control (311.95 ± 94.13 µg/mL) ($p < 0.001$). A strong positive correlation was observed between fetuin-A concentrations with serum hs-CRP concentrations in the diabetic individuals but not in the controls.

CONCLUSIONS Diabetic Iraqi women have higher inflammatory markers (fetuin-A and hs-CRP) than non-diabetic women. A strong association was observed for these inflammatory biomarkers and glycemic control in diabetic subjects.

KEYWORDS inflammatory biomarkers, type 2 diabetes, fetuin-A, high sensitivity C-reactive protein

INTRODUCTION

Diabetes is a chronic disease that represents a major health problem and a great challenge to healthcare provision worldwide. Presently, there is great attention toward diabetes due to its growing prevalence. Because of this rapid rise, the disease was classified as “epidemic” by the Centres for Disease Control and Prevention in the USA in 2007. The type 2 diabetes mellitus population world-wide is predicted to rise to 629 million by 2045 (1). Among all types of diabetes, type 2 diabetes represents the most common form, accounting for 90–95% of all cases. The aetiology of the condition involves interaction between both genetic and environmental factors. According to Genome-Wide Association Studies

(GWAS), the risk of type 2 diabetes is related to more than 80 loci (2). During the last decade, epigenetic mechanisms have been proposed as being involved in disease development and progression. Environmental factors such as obesity and sedentary lifestyle are considered the most common factors increasing the risk of getting the disease. These factors also contribute substantially to the development of insulin resistance. Cumulative evidence has shown that inflammation plays a crucial role in the development of insulin resistance. Many inflammatory cytokines, such as TNFα, IL-32 and IL-6, have been shown to be associated with insulin resistance (3). Improved understanding of the exact mechanisms of developing diabetes, findings about other biomarkers and their interaction could potentially help improve disease management or even prevention. A dual effect of inflammation on type 2 diabetes has been observed: inflammation has been shown to cause insulin resistance, and in patients with overt diabetes, it also causes deterioration of glycemia as reflected by increasing levels of glycated haemoglobin- HbA1c (4).

High sensitivity C-reactive protein (hs-CRP) represents an important sensitive inflammatory marker of tissue damage and is used as an indicator which links inflammation with type 2 diabetes. Another emerging inflammatory biomarker of interest is fetuin-A, a Heremans Schmid alpha-2 glycoprotein (AHSG) that is secreted by liver cells (5).

In-vitro studies, fetuin-A has been shown to cause insulin resistance by inhibiting insulin receptor's tyrosine kinase, leading to impairment of insulin signalling in in muscle and fat cells (6).

Epidemiologically, in several prospective studies a link between a high level of fetuin-A and diabetes incidence has been reported (7, 8).

Our study aimed to evaluate the influence of inflammatory markers (hs-CRP and fetuin-A) on glycemic control in Iraqi women patients with type 2 diabetes, and to examine the correlation of these markers with indices of glycemic evaluation.

METHODS

Subjects

This case-control study included a total 90 female individuals aged 36-66 years of whom 45 were patients with type 2 diabetes recruited during routine visits to the specialized endocrine clinic of Dyala Teaching Hospital, Dyala, Iraq, between October 2020 and March 2021. An additional 45 age-matched healthy female subjects with no history of diabetes as confirmed by normal fasting plasma glucose and normal glycated hemoglobin levels were included as controls.

Exclusion criteria included women of other nationalities (non-Iraqis) and women with other endocrine abnormalities or inflammatory conditions such as chronic arthritis, chronic kidney disease and heart disease. The study was ethically approved according to national and/or international rules by the scientific committee of the Department of Chemistry and Biochemistry, College of Medicine, Mustansiriyah University. Verbal and signed consent of agreement were obtained from all participants.

Body mass index (BMI) of participants was calculated using the formula weight (kg)/square height (m^2).

For blood analysis, a fasting venous blood sample was obtained from all participants. HbA1c was measured using anti-coagulated whole blood (SD A1cCareTM System, Biosensor, Suwon-si, South Korea).

Spectrophotometric methods were used to examine serum samples including biochemical tests, fasting blood glucose (FBG), total cholesterols (TC), triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) (Biolabo, Maizy, France).

Fetuin-A measurement was performed by enzyme-linked immune sorbent assay using ELISA kits from Abcam Company, Cambridge, UK (ab108855-fetuin A (AHSG) Human ELISA Kit and Human hs-CRP: ELISA Kit, Catalog No: MBS2506093-96T, MyBiosource, San Diego, San Diego, USA.

Data analysis

Data was analyzed using GraphPad Prism 8.0.2 (263). A mean ± standard deviation was used to describe the data. After testing data distribution using suitable tests, the significance of difference was tested using Student's t-test.

Correlation analysis was performed using Pearson's correlation for variables and the t-test was used for determining the statistical significance of the correlations. The correlation coefficient values (r) were either positive (having direct correlation), or negative (having inverse correla-

tion). Statistical significance was considered to be $p < 0.05$.

RESULTS

The demographic and clinical characteristics of subjects enrolled in the study are presented in Table 1. No age or BMI differences were observed between type 2 diabetes and healthy subjects. Both lipid profiles and glycemic indexes showed significant differences between groups ($p < 0.0001$).

The graph in Figure 1 is a representative of the comparison study of biomarkers between patients and controls. fetuin-A level was significantly higher in the diabetic group compared to the healthy control ($p < 0.0001$). The same observations were conducted regarding hs-CRP, total cholesterol, triglycerides and LDLc. The level of HDL was significantly lower in the diabetic group compared to the control $p < 0.0001$.

The correlation analysis of study parameters with fetuin-A in diabetic patients and control is presented in Figure 2. A positive correlation was observed between fetuin-A and both FBS and HbA1c in diabetics: r = 0. 723, $p < 0.0001$ and r = 0.811, respectively, $p < 0.0001$. No such correlation was observed in the controls. A positive correlation between fetuin-A and BMI was observed in both groups, but it was higher in the diabetics compared to control. A positive correlation was detected between Fetuin-A and age in the control group r = 0. 482, $p < 0.05$, but no such correlation was observed in the type 2 diabetic patients.

Figure 3 presents the correlation analysis of the study parameters with serum high sensitivity C-reactive protein in both diabetic patients and controls. A positive correlation was observed between hs-CRP and both FBS and HbA1c in the diabetics: r = 0. 826, $p < 0.0001$ and r = 0.781, $p < 0.0001$, respectively. No such correlation was observed in the controls. A positive correlation was observed in both groups between hs-CRP and BMI, but it was higher in the diabetics compared to the control. A positive correlation was detected between hs-CRP and age in both the control group and the type 2 diabetic patients.

Table 1. Anthropometric characteristics of the study subjects

	Type 2 diabetes patients No (45)	Healthy No (45)	*p*-value
Age (years)			
Mean±SD (range)	47.98±8.43 (29-68)	48.32±7.34 (36-66)	0.073^{ns}
BMI (kg/m^2)			
Mean±SD (range)	27.48±2.133 (22.61-32.14)	27.38±2.02 (22.11-30.93)	0.8185^{ns}
BMI (kg/m^2)			
Normal (18.5-24.9)	4 (8.9%)	8 (17.8%)	
Overweight (25-29.9)	37 (82.2%)	30 (66.6%)	
Obese (≥30)	4 (8.9%)	7 (15.6%)	
FBG (mg/dL)			
Mean±SD (range)	227±74.39 (111-365)	88.55±15.83 (65-125)	0.0001*
HbA1c %			
Mean±SD (range)	8.82±2.53 (4.25-13.56)	4.46±0.75 (3.1-6.84)	0.0001*
Total cholesterol (mg/dL)			
Mean±SD (range)	278.5±56.22 (166-422)	167.5±23.60 (122-237)	0.0001*
TGL (mg/dL)			
Mean±SD (range)	302.8±117.7 (141-631)	187±27.14 (129-260)	0.0001*
LDLc (mg/dL)			
Mean±SD (range)	188.2±62.67 (62.6-342.6)	98.16±24.21 (35-161)	0.0001*
HDLc (mg/dL)			
Mean±SD (range)	29.8±10.6 (17-54)	42.59±10.46 (30-67)	0.0001*

*Significant difference between two independent means using Students-t-test at 0.05 level; ^{ns}means no significant difference, * means there is significant difference

BMI, body mass index; FBS, fasting blood glucose; TGL, total triglycerides; LDLc, low density lipoprotein cholesterol; HDLc, high density lipoprotein cholesterol

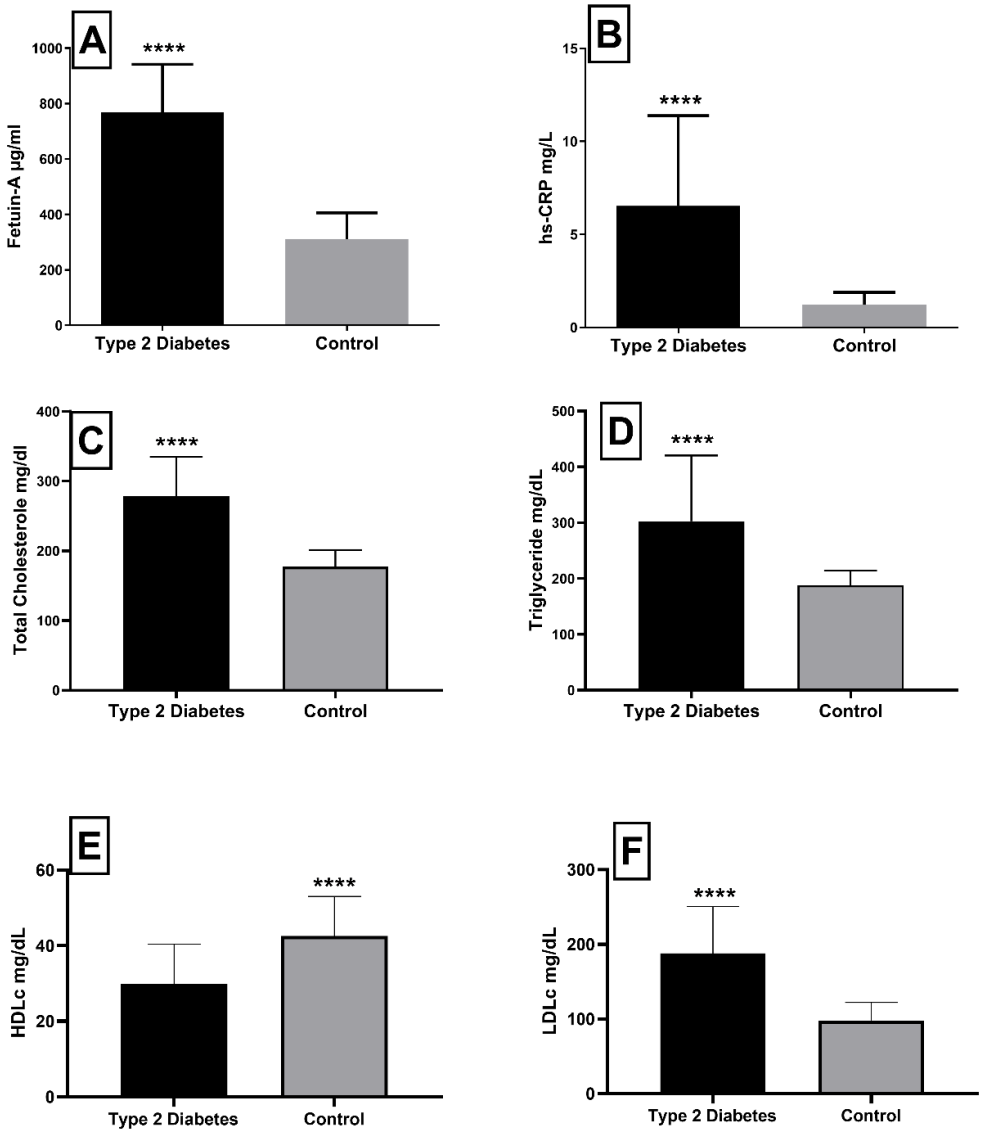

Figure 1. Graphs representative of the means measures for groups of the study (black bars - type 2 diabetes group; gray bars - healthy control group. A) represents the results of fetuin-A, B) represents serum hs-CRP, C) represents total cholesterol, D) represents triglycerides, E) for high density lipoprotein cholesterol and F) for low density lipoprotein cholesterol. Differences between means calculated by unpaired student t test; **** indicates p <0.0001

DISCUSSION

To our knowledge, this is the first study investigating the role fetuin-A and hs-CRP in glycemic control in Iraqi type 2 diabetes patients. The main results obtained from the current study are that statistically significantly higher levels of both fetuin-A and hs-CRP were observed in the diabetic group compared to the healthy controls. Furthermore, high significant positive correlations were observed between the level of glycemia and both fetuin-A and hs-CRP.

Glycemic control is the major target for management of type 2 diabetes. Advanced glycation end products (AGEs) like HbA1c represent the best reflection of the level of glycemic control. More than three decades ago, the American Diabetes Association recommended the use of HbA1c for routine monitoring of patients with diabetes (9). In addition, a significant reduction in HbA1c percentage has been shown to significantly reduce the onset and progression of diabetic associated complications (10, 11). Chronic inflammation is a direct cause and results in the complications associated with type 2 diabetes (12).

High HbA1c that results from chronic hyperglycemia can increase expression of pro inflammatory factors and initiate signals that lead to hepatic CRP production in diabetic and obese

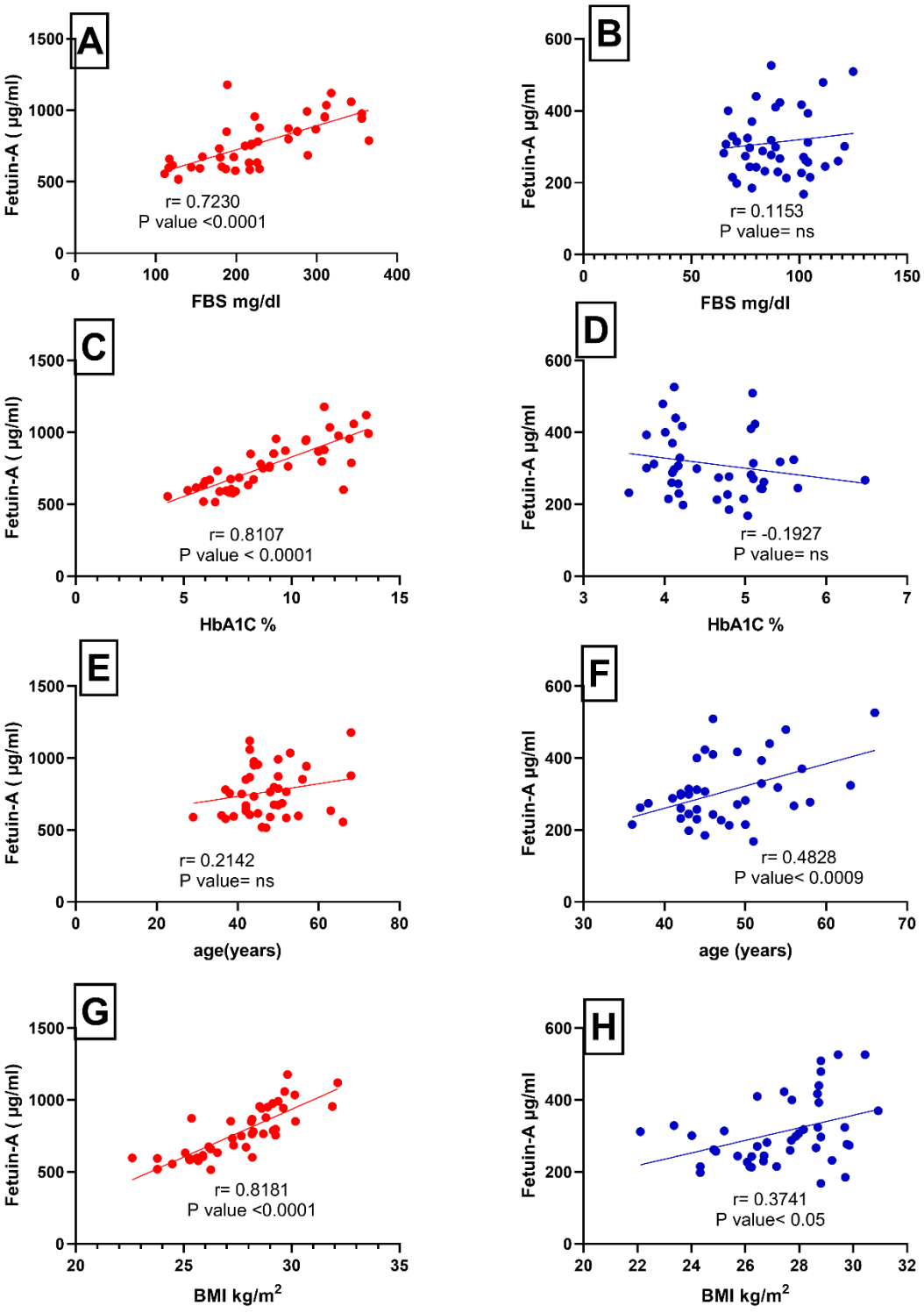

Figure 2. Graphs representative of correlation analysis of serum fetuin-a level with fasting blood sugar (FBS), glycated hemoglobin (HbA1c), age, and body mass index (BMI): left panel in red for the type 2 diabetes group and right panel in blue for the control group. A) and B) are correlation analyses of both type 2 diabetes and control groups for serum fetuin-a and FBS in mg/dL; C) and D) are correlation analyses for fetuin-a and HbA1c%; E) and F) are fetuin-a and age in years; G) and H) are fetuin-A and BMI in kg/m^2

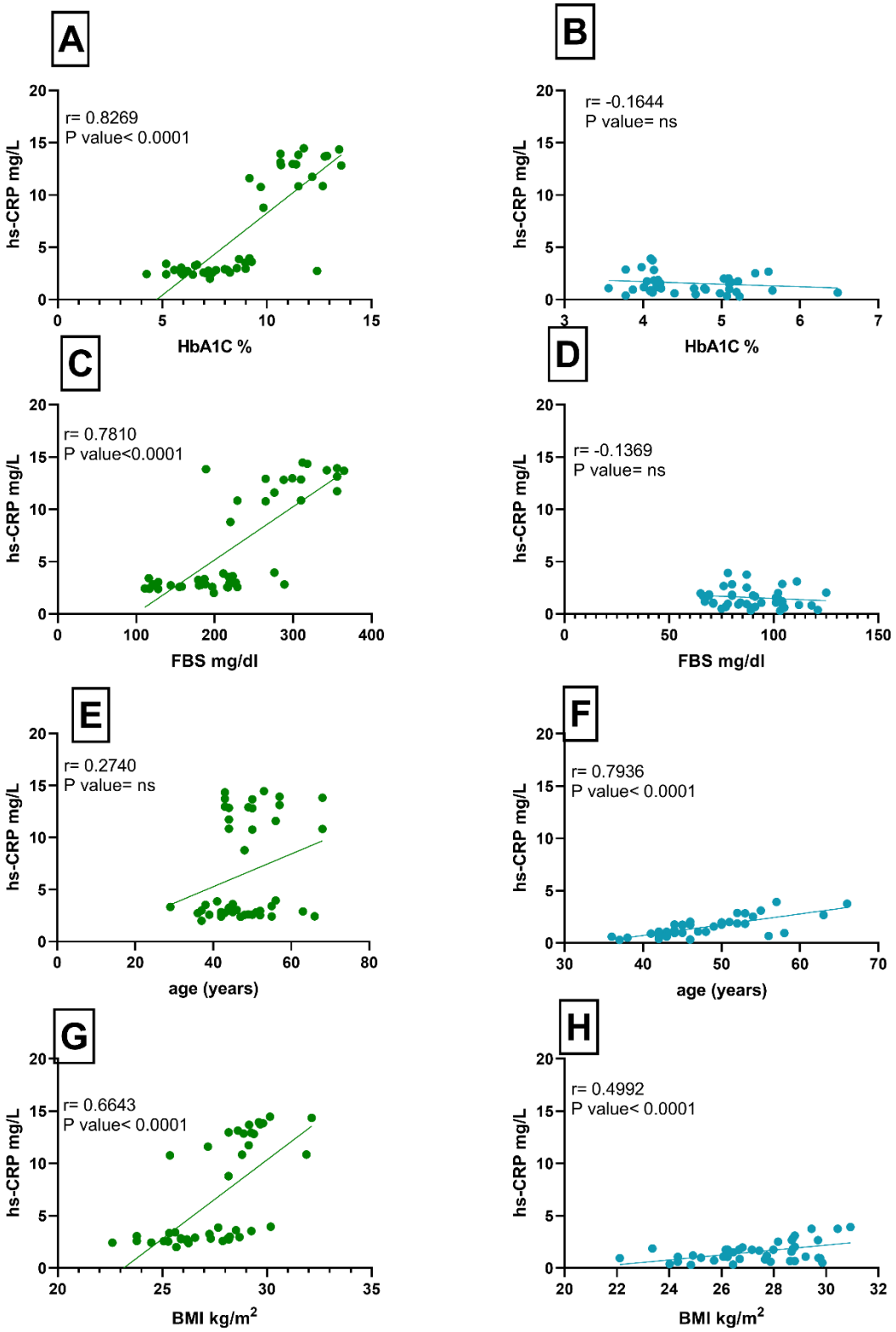

Figure 3. Graphs representative of correlation analyses of serum high sensitivity C-reactive protein (hs-CRP) level with fasting blood sugar (FBS), glycated haemoglobin (HbA1c), age, and body mass index (BMI) in the left panel in green for the type 2 diabetes group and in the right light blue for the control group. A) and B) are correlation analyses of both type 2 diabetes and control groups for serum hs-CRP and FBS in mg/dL; C) and D) are hs-CRP and HbA1c %; E) and F) are hs-CRP and age in years; G) and H) are hs-CRP and BMI in kg/m^2

subjects. Tan and Chow suggested that proinflammatory cytokine-like IL-6, tumor necrosis factor α and IL-1 are all primary signals that act on tissues through their downstream CRP (13).

In the current study, hs-CRP as a sensitive inflammatory marker was shown to be high in the diabetic group 3.1 ± 0.59 mg/dL compared to the control 1.22 ± 0.66 mg/dL and was significantly correlated $p < 0.001$ with the marker of chronic hyperglycemia, HbA1c, as well as with body mass index BMI as a contributor to insulin sensitivity.

Additionally, a large body of evidence has shown that an elevated concentration of inflammatory markers in patients with type 2 diabetes affects can affect insulin sensitivity and function. Examples of these inflammatory markers include C-reactive protein (CRP) (14), fibrinogen (15) and thrombin (16). The same observation was noted in our study that hs-CRP in type 2 diabetes was significantly higher than that observed in controls. The value of hs-CRP in the diabetic group put them at high risk for diabetic CVD complications.

Fetuin-A, a hepatic-produced glycoprotein (hepatokine), performs a variety of functions in humans, including skeletal, metabolic and anti-inflammatory functions (17). The focus of the current study is the association of fetuin-A with type 2 diabetes and glycemia. Previous studies have shown the existence of association of risk of type 2 diabetes with elevated fetuin-A levels (7, 18). The proposed mechanisms of this association include, firstly, that fetuin-A has been shown to inhibit insulin-stimulated insulin receptor tyrosine kinase which then alters the insulin signaling pathway and then leads to insulin resistance (19, 20). Secondly, genetic-based association studies described in many scientific papers show that the gene encoding fetuin-A represents type 2 diabetes susceptibility loci (21). In addition, fetuin-A has been shown to be associated with obesity and inflammation, the major risk factors for type 2 diabetes. Both experimental and clinical data have shown the role of fetuin-A in obesity (14).

In the current study, the serum level of fetuin-A in the diabetic group (768.7 ± 173.03 μg/mL) was significantly higher than that of the control (311.95 ± 94.13 μg/mL) ($p < 0.001$). These results are in concordance with results of a previous study by Song (22) as well as Lorant and Grujicic (23). Furthermore, in the current study a positive correlation was observed between fetuin-A and the level of glycemia represented by HbA1c and fasting glucose. These results are in agreement with a study by Yin (24) performed on newly diagnosed type 2 diabetes individuals and another study which included women with gestational diabetes mellitus (25).

The association of fetuin-A concentrations with serum hs-CRP concentrations is still controversial. On one hand, serum CRP concentrations have been found to be positively associated with metabolic syndrome and fetuin-A level, and these studies have also implicated fetuin-A in the pathogenesis of subclinical inflammation (26). On the other hand, studies such as that performed by Ombrellino (27) as well as Song (22) showed no correlation or even that the serum level of fetuin-A can modulate or downregulate the inflammatory response. In our study, a strong positive association was observed between fetuin-A concentrations with serum hs-CRP concentrations in diabetic individuals, but no such relation was found in the controls. These results provide additional evidence supporting previous studies which have observed that inflammation and fetuin-A are involved in the pathogenesis and progression of type 2 diabetes and its complications.

CONCLUSIONS

Fetuin-A levels are higher in type 2 diabetic Iraqi women patients compared to non-diabetic controls. The increased level of fetuin-A in diabetic groups is associated with glycemic control and with the level of systemic inflammation. The high level of inflammatory markers could have a role in diabetic complications and could be considered in modulating the modality of therapy in those patients.

Recommendations

Further study exploring the mechanisms that involve lower glycemic control with elevated fetuin-A levels and the effects of different treatment regimens on these inflammatory factors is needed.

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CONFLICTS OF INTEREST

We have no potential conflicts of interest relevant to this article.

AUTHOR CONTRIBUTION

The work performed by all the authors equally.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

INSTITUTIONAL REVIEW BOARD STATEMENT

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of [College of Medicine, Mustansiriyah University] (Approval No: 20234, Date: 22/10/2024)

INFORMED CONSENT STATEMENT

Written informed consent was obtained from all participants after explaining the study purpose, procedures, risks, and benefits.

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