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Fetuin-A Levels and Their Relationship with Insulin Resistance and Low-grade Inflammation

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ABSTRACT

Objective: *This work was aimed to evaluate serum Fetuin-A levels and its probable association with insulin resistance and other relevant metabolic and inflammatory parameters in patients with insulin resistance (IR) and type 2 diabetes mellitus (T2DM).* ***Method:*** *A cross-sectional analytic study was carried out at Tikrit Teaching Hospital from August 2025 to January 2026. Two hundred and fifty subjects, 25–55 years in age were included in the study as follows – healthy (n = 50), insulin resistant but with no overt diabetes mellitus (n = 100) and type two diabetic patients with coexisting insulin resistance (T2D-IR, n = 100). The serum Fetuin-A level, fasting plasma glucose (FPG), fasting insulin, glycosylated hemoglobin (HbA1c), lipid profile, inflammatory markers including high sensitivity C-reactive protein (hs-CRP), IL-6 and TNF-a, as well as liver enzymes were determined. Insulin resistance was evaluated based on the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).* ***Results:*** *The serum levels of Fetuin-A were significantly increased in both insulin resistant subjects with the highest level in type 2 diabetes mellitus patients ($p < 0.001$). Serum Fetuin-A levels were positively associated with HOMA-IR, fasting insulin, inflammatory parameters, triglycerides, body mass index and liver enzymes and inversely correlated with HDL-C.* ***Novelty:*** *The results of this study corroborate the potential value of Fetuin-A as a biomarker for metabolic disturbance and disease progression. High circulating levels of Fetuin-A strongly correlated with insulin resistance, chronic inflammation and metabolic profile unfavourability.*

INTRODUCTION

Insulin resistance is a central pathophysiological feature of three major diseases: type 2 diabetes mellitus, obesity, and metabolic syndrome. The presence of overt metabolic abnormalities, diminished glucose uptake in response to insulin, compensatory hyperinsulinemia and insulin resistance within peripheral tissues is evidence [1]. Besides increasing the risk of CVD, IR also stimulates prediabetes and type 2 diabetes-related symptoms including dyslipidemia, endothelial dysfunction, and hyperglycemia. Therefore, it is a great risk to public health of the world nowadays [2;3].

Low-grade chronic inflammation is now emerging as one of the key players in IR's etiology and onset. An effect of hypertrophy of the adipose tissue is the overproduction in obese subjects of pro-inflammatory cytokines, such as IL-6 and TNF-α [4]. These inflammatory mediators accentuate metabolic problems through downregulation of insulin signaling but chemokines initiated via TLR4 functions as a link between metabolism and inflammation [5]. Insulin resistance and type 2 diabetes mellitus are the

most frequent causes of elevation in high-sensitivity C-reactive protein (hs-CRP), a prototypic marker associated with this subclinical inflammatory state [6;7].

The liver is an essential endocrine organ because it secretes hepatokines, which not only regulate metabolic equilibrium but are also released from interactions with the products of adipose tissue [8]. Due to its dual function in inflammation and regulation of disorder metabolism, Fetuin-A (an α-2-Heremans-Schmid glycoprotein; one of the hepatokines in super-natant) was extensively investigated [9]. Most of the fetain-A a small molecule which impacts insulin sensitivity and inflammation that enters the blood comes from the liver [10].

Fetuin-A prevents insulin from signaling properly in adipose and muscle tissue by inhibiting its receptor tyrosine kinase activity, studies in both animals and humans have found [11]. It has been reported that high levels of Fetuin-A are correlated with insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus and metabolic diseases [12]. Toll-like receptor 4 (TLR4) endogenous ligand (fetalin-A), is involved in free fatty acid-induced inflammation. Fatty acid synthesis, inflammation and insulin resistance are interconnected [13;14].

Fetuin-A was not associated with glucose metabolism, but was related to cardiovascular and lipid risk factors. Blood levels of Fetuin-A are inversely correlated with levels of HDL-C and LDL-C/LDL cholesterol in addition to positively related with blood triglyceride concentrations [15]. According to these observations, Fetuin-A might be a mediator of the development of atherogenic dyslipidemia in insulin-resistant era. The observation that Fetuin-A is related to mild liver damage and fatty infiltration adds further evidence that it is a liver-derived protein with metabolic effects [16]. While there is mounting evidence linking Fetuin-A to metabolic diseases, our understanding of the interplay between insulin resistance, low-grade inflammation, Fetuin-A, and other metabolic variables remains incomplete across the many phases of metabolic dysfunction. We can learn more about the timing and significance of Fetuin-A level changes by comparing insulin-resistant individuals who do not have diabetes with those who have chronic type 2 diabetes mellitus (DM) [17]. The potential of Fetuin-A as a metabolic risk prediction biomarker and an early indicator of illness can be further understood with the aid of this work. We compared insulin-resistant people (not including diabetics) and patients with Type 2 Diabetes Mellitus (T2DM) by analyzing blood Fetuin-A levels and how they correlated with insulin resistance and low-grade inflammatory markers.

RESEARCH METHOD

Study Design and Setting

This was a cross-sectional analytical study done at the Tikrit Teaching Hospital in Salah Al-Din Governorate, Iraq. The research was conducted from April 2025 to January 2026. The objective of the study was to examine the relationship among serum Fetuin-A levels, insulin resistance, and low-grade inflammatory markers in individuals.

Study Population and Sample Size

The research comprised men and women aged 25 to 55 years. A sample of 250 patients was gathered and categorised into three principal categories. Group I (the control group) was made up of 50 people who looked healthy, had normal FBG levels, and showed no signs of insulin resistance or inflammatory disorders.

The patients (n = 200) were divided into two groups. Group II consisted of 100 non-diabetic insulin-resistant individuals with elevated HOMA-IR while maintaining normal to impaired fasting glucose levels. Group III consisted of 100 individuals diagnosed with type 2 diabetes mellitus characterized by insulin resistance. This classification facilitated the examination of Fetuin-A concentrations in connection to varying levels of metabolic disturbance and its correlation with insulin resistance (IR) and low-grade inflammation.

Inclusion and Exclusion Criteria

This study included participants aged 30-65 years. The study group encompassed cases with documented insulin resistance, regardless of the diagnosis of type 2 diabetes mellitus. Control participants were apparently healthy subjects with normal fasting blood glucose levels and no clinical evidence of insulin resistance.

The exclusion criteria included subjects with acute or chronic inflammatory disease, hepatic or renal dysfunction, cardiovascular diseases, malignancy and autoimmune diseases in pregnancy and who were treated with anti-inflammatory or immunosuppressant agents.

Data Collection and Clinical Assessment

A thorough physical examination and evaluation of medical history were components of each participant's full clinical assessment. The researchers measured and recorded anthropometric variables including body mass index (BMI). After an 8–12 hour fast, the patient's blood was collected from veins in a sterile setting.

Laboratory Investigations

The individuals were instructed to fast for eight to twelve hours before to blood sampling. Specimens of venous blood were collected under aseptic conditions in their designated tubes and promptly sent to the laboratory for standard testing. Centrifuged serums were stored at the proper temperature from the time of collection until analysis.

Serum Fetuin-A concentrations were determined by the manufacturer according to commercial assay kits (R&D Systems, Minneapolis, USA). CVs (standing for Assay sensitivity, intra- and inter-assay) proved the precision and reproducibility of these parameters.

Fasting plasma glucose (FPG) was assayed by the enzymatic glucose oxidase method and fasting serum insulin level was assayed using the Chemiluminescent immunoassay. Insulin resistance was estimated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) formula.

Furthermore, in order to obtain a more comprehensive metabolic profile we also examined the hepatocytes for glycated hemoglobin (HbA1c), an indicator of long-term glucose control, particularly relevant in diabetics. End-point enzymatic colorimetric methods were also used to evaluate the lipid profile, (Serum total cholesterol (TC),

triglycerides (TG), with high-density lipoprotein-cholesterol (HDL-C) and low density-lipoprotein-cholesterol (LDL-C)], due to the well elegant correlation between dyslipidemia, insulin resistance and Fetuin-A activity.

We examined high-sensitivity C-reactive protein (hs-CRP) levels as marker of low-grade systemic inflammation by means of a highly sensitive immunoturbidimetric assay. Levels of serum IL-6 and tumor necrosis factor-alpha (TNF-α) were detected by ELISA to reflect the inflammatory process correlated with metabolic alteration.

Fetuin-A is made in the liver, so standard liver function tests (alanine transaminase [ALT] and aspartate transaminase [AST]) were also performed to exclude obvious liver disease or associations between liver health and Fetuin-A levels. All tests were performed in the Tikrit Teaching Hospital central laboratory using standardized procedures and calibrated instruments to ensure consistency of measurements.

Statistical Analysis

Statistical analyses of data were conducted using appropriate tools. Continuous data were presented as mean ± standard deviation. We used the right statistical procedures to compare the two groups and looked at how the levels of Fetuin-A were connected to insulin resistance and inflammatory markers. P values less than 0.05 were deemed significant.

Ethical Considerations

The local ethical committee of Tikrit Teaching Hospital gave the study protocol the green light. Before enrolling, all participants gave their written consent, and the study kept all participant data private at all times.

RESULTS AND DISCUSSION

Results

General Characteristics of the Study Population

For the present study, 250 sets of subjects were included - healthy controls (Group I), non-diabetic insulin resistant (InsR) patients (Group II) and type 2 diabetic InsR patients (Group III). There were no significant differences in age and sex distribution between the three groups, indicating a successful matching. Nevertheless, substantial differences in anthropometric and metabolic factors still prevailed between the study groups (Table 1).

Table 1. Demographic and anthropometric characteristics of the study groups.

Parameter	Group I (Control) n=50	Group II (IR non-DM) n=100	Group III (T2DM + IR) n=100	P-value
Age (years)	41.2 ± 7.3	42.6 ± 6.9	43.1 ± 7.1	0.312
Male/Female	26 / 24	52 / 48	54 / 46	0.874
Weight (kg)	68.4 ± 9.1	81.7 ± 10.4	85.9 ± 11.2	<0.001
BMI (kg/m²)	23.6 ± 2.8	29.4 ± 3.1	31.2 ± 3.6	<0.001

Glycemic Status and Insulin Resistance

Fasting plasma glucose, fasting insulin, HbA1c and HOMA-IR values increased gradually from healthy subjects to non-diabetic patients with IR to T2DM patients and were highest in the latter group. These findings imply impairment of glycemic control and insulin sensitivity in the studied populations (Table 2).

Table 2. Glycemic parameters and insulin resistance indices.

Parameter	Group I	Group II	Group III	P-value
FPG (mg/dL)	89.6 ± 7.4	108.3 ± 11.2	168.7 ± 32.5	<0.001
Fasting Insulin (µIU/mL)	7.8 ± 2.1	18.4 ± 4.6	24.9 ± 6.2	<0.001
HOMA-IR	1.7 ± 0.5	4.9 ± 1.3	10.4 ± 3.1	<0.001
HbA1c (%)	5.2 ± 0.4	5.9 ± 0.6	8.1 ± 1.2	<0.001

Serum Fetuin-A Levels among Study Groups

Insulin-resistant individuals exhibited significantly higher serum Fetuin-A levels in comparison to healthy controls. The highest levels were found in people with type 2 diabetes mellitus, which suggests that Fetuin-A is closely linked to the severity of metabolic dysfunction (Table 2 ana Figure 1).

Table 3. Serum fetuin-a levels in the study groups.

Parameter	Group I	Group II	Group III	P-value
Fetuin-A (ng/mL)	245.3 ± 38.6	368.7 ± 54.1	492.6 ± 67.9	<0.001

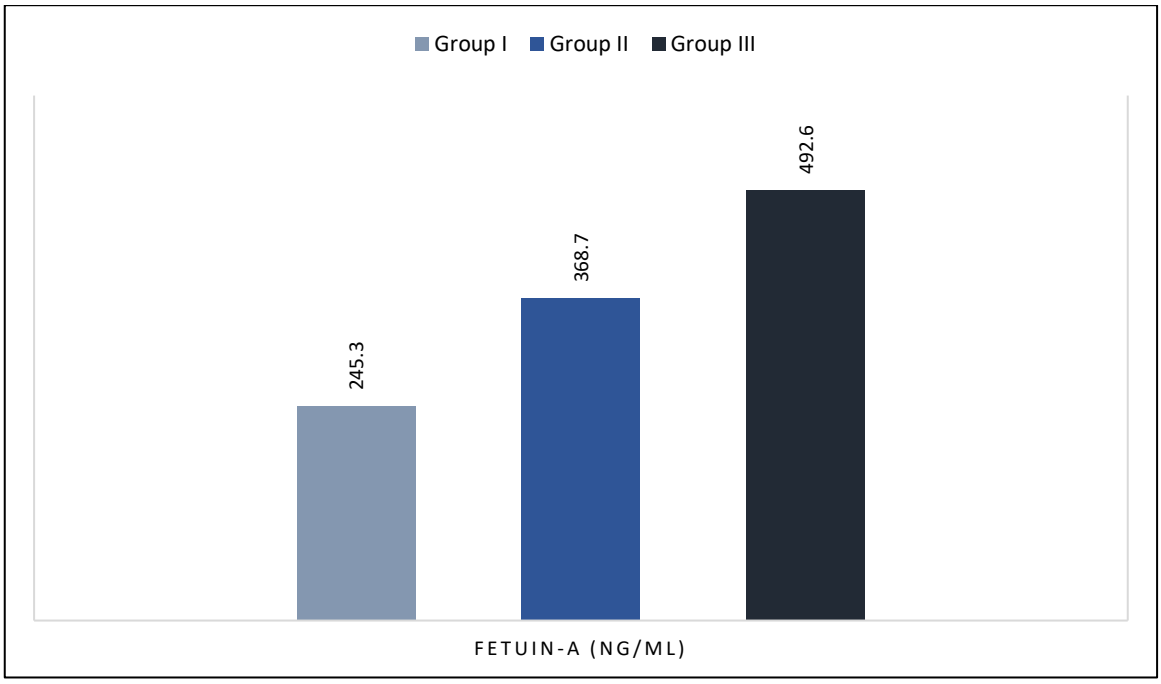

Figure 1. Fetuin-A Levels in studied groups.

Lipid Profile Analysis

Patients with disordered glucose metabolism/insulin resistant individuals were characterized by further enhanced atherogenic dyslipidemia than those without diabetes mellitus and insulin resistance. The serum triglyceride and low-density lipoprotein cholesterol (LDL-C) concentrations were dramatically increased, whilst high-density lipoprotein cholesterol (HDL-C) levels were notably decreased, with the most marked effect in Group III (Table 4).

Table 4. Lipid profile parameters.

Parameter (mg/dL)	Group I	Group II	Group III	P-value
Total Cholesterol	172.5 ± 24.6	201.8 ± 31.7	228.4 ± 36.9	<0.001
Triglycerides	118.6 ± 29.1	176.4 ± 42.8	221.9 ± 51.3	<0.001
HDL-C	49.7 ± 6.4	41.3 ± 5.9	36.1 ± 5.2	<0.001
LDL-C	101.4 ± 21.7	124.8 ± 28.4	149.6 ± 33.5	<0.001

Inflammatory Markers and Cytokines

Surrogates of low-grade systemic inflammation increased progressively between the groups. Those with insulin resistance had a higher hs-CRP, IL-6, and TNF-α than the insulin sensitive group, and the highest level could be found in diabetes mellitus patients. These results underline the indeed inflammatory base of insulin resistance (Table 5).

Table 5. Inflammatory markers among study groups.

Parameter	Group I	Group II	Group III	P-value
hs-CRP (mg/L)	1.2 ± 0.6	3.4 ± 1.2	5.8 ± 2.1	<0.001
IL-6 (pg/mL)	2.1 ± 0.7	4.8 ± 1.4	7.2 ± 2.0	<0.001
TNF-α (pg/mL)	3.6 ± 1.1	6.9 ± 1.9	9.8 ± 2.7	<0.001

Liver Function Tests

Even though alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels stayed within the normal range, people with diabetes mellitus and insulin resistance had much higher levels than healthy controls, which showed that their livers were not working properly (Table 6).

Table 6. Liver function parameters.

Parameter (U/L)	Group I	Group II	Group III	P-value
ALT	22.4 ± 6.1	31.7 ± 8.4	38.9 ± 10.6	<0.001
AST	21.1 ± 5.4	28.3 ± 7.2	34.6 ± 9.1	<0.001

Correlation between Serum Fetuin-A and Metabolic and Inflammatory Parameters

To examine if blood Fetuin-A levels were associated with the investigated metabolic and inflammatory indices in the study population, correlation analysis was conducted.

An inverse relationship of fetain-A with protective lipid fractions was found but had a strong good correlation with indices of insulin resistance, glycemic control, inflammatory markers, lipid profile in the blood and anthropometrics. In conclusion, these data underscore Fetuin-A as a link between insulin resistance, inflammation and increased metabolic risk factors (Table 7).

Table 7. Correlation of serum fetuin-a with metabolic, inflammatory, and anthropometric parameters.

Parameter	Correlation Coefficient (r)	P-value
Fasting Plasma Glucose	0.61	<0.001
Fasting Insulin	0.73	<0.001
HOMA-IR	0.79	<0.001
HbA1c	0.67	<0.001
Body Weight	0.58	<0.001
BMI	0.71	<0.001
Triglycerides	0.65	<0.001
Total Cholesterol	0.49	<0.001
LDL-C	0.57	<0.001
HDL-C	–0.54	<0.001
hs-CRP	0.76	<0.001
IL-6	0.74	<0.001
TNF-α	0.69	<0.001
ALT	0.46	<0.001
AST	0.42	<0.001

Discussion

Fetuin-A is a primary hepatokine for metabolic derangement, and there is substantial evidence that it is implicated in the elevated blood Fetuin-A concentrations seen in IR patients, especially those with type 2 diabetes [18]. Peripheral insulin resistance and reduced intracellular insulin signaling are caused by fetain-A's down-regulation of insulin receptor tyrosine kinase (IRTK) [19]. This study indicates that increased Fetuin-A levels are significantly linked to the incidence and severity of metabolic illnesses rather than being a separate pathogenic condition. Metabolic problems were more common in patients with these elevated levels.

Both fasting insulin and HOMA-IR were positively and significantly linked with fetain-A levels. Fetuin-A blocks insulin-stimulated glucose absorption in adipose tissue and skeletal muscle, as seen in animal research and human clinical trials [20]. Insulin resistance and chronic high blood sugar, which can lead to type 2 diabetes, may be influenced by Fetuin-A because of its strong relationship to HbA1c.

The association of Fetuin-A with low-grade systemic inflammatory marker such as hs-CRP, TNF-α and IL-6 was observed in our present study which is very significant cornerstone. The Toll-like receptor 4 (TLR4) pathway, through which lipids provoke the

inflammatory response, is potentially modulated by endogenous Fetuin-A [21]. This does not only account for the association between Fetuin-A and pro-inflammatory cytokines, but also indicates that Fetuin-A may interject into the relationship of metabolic stress and chronic low-grade inflammation.

Alterations in lipid metabolism, which are frequently associated with both diabetes and insulin resistance, suggest that Fetuin-A is a critical metabolic factor. Fetain-A can be involved in hyperlipidemia as a potential trigger due to its direct relationships with triglycerides, total cholesterol and LDL-C, and reverse a relationship with HDL-C. These findings indicate that Fetuin-A, in insulin resistant and type 2 diabetic individuals, may play a pathogenic role in the proneness for cardiovascular disease.

Furthermore, anthropometric measurements like BMI and weight significantly correlated with increased Fetuin-A levels. Insulin resistance and systemic inflammation are largely influenced by the state of overweight [22]. Based on the most recent reported results [23;24], increased hepatic activity and inflammatory signaling are implicated in an indirect association between increased adiposity and Fetuin-A. Obesity, insulin resistance, hepatic steatosis and metabolic inflammation are all linked to one another, and our finding upholds this principle.

The elevated proportion of insulin-resistant and diabetic subjects, along with increased values in these two groups, and significant associations between them and Fetuin-A may suggest subclinical liver damage, even though hepatic enzyme concentrations were within the clinically accepted ranges. Since the liver is the primary producer of Fetuin-A, even moderate levels of hepatic dysfunction in insulin resistant people may lead to an overproduction of Fetuin-A and worsen metabolic problems.

The results indicate that Fetuin-A is a key negative regulator that links insulin resistance, inflammation, dyslipidemia, and other metabolic abnormalities associated with obesity. Despite the limitations of our study's cross-sectional design, the consistent and robust relationships between Fetuin-A and metabolic risks suggest that Fetuin-A might be used as an early biomarker for adiposity if it behaves pathologically. The temporal connections of high Fetuin-A levels with the development of insulin resistance and hyperglycemia need to be determined by long-term and prospective research.

CONCLUSION

Fundamental Finding : The study demonstrates that serum Fetuin-A levels are significantly elevated in patients with insulin resistance, reaching the highest levels in type 2 diabetes, and showing strong associations with insulin resistance markers, low-grade inflammation, and abnormal fat accumulation, highlighting its central role in metabolic dysregulation. **Implication :** Fetuin-A may function as a mechanistic link between metabolic stress and chronic inflammation and could serve as a promising biomarker for early diagnosis and risk stratification in insulin-resistant individuals and related metabolic disorders. **Limitation :** The study does not establish causal relationships among Fetuin-A, inflammatory processes, and metabolic abnormalities. **Future Research :** Prospective studies are required to clarify causal pathways and to

explore beta-cell products as potential therapeutic targets for the prevention and treatment of metabolic diseases.

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