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Original Article

Fetuin-A as Predictor of Insulin Resistance in Diagnosed Case of Prediabetic in Association with Glycaemic Indices

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Abstract

Background: Prediabetes is a metabolic disorder that is characterized by the impaired glucose fasting condition and/or glucose tolerance, representing a state of intermediate between diabetes and normal glucose metabolism. It is associated with multiple metabolic disturbances and elevated risk of diabetes mellitus. Fetuin-A, a multifunctional hepatokine and adipokine, plays important function in pathogenesis of several chronic diseases and insulin resistance. This research aimed to assess the serum levels of Fetuin-A in individuals with prediabetes in Duhok City. This study also aimed to examine the relationship between key metabolic risk factors and Fetuin-A levels. **Methods:** A cross-sectional study was carried out involving 150 participants, aged 18–75 years, including 75 prediabetic and 75 Apparently Healthy subjects, recruited between September 2024 and July 2025. Prediabetes was diagnosed based on the criteria established by the American Diabetes Association (ADA). Demographic, clinical, and biochemical data were collected, including fasting blood glucose (FBG), 2-hour oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1c), insulin levels, Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), and serum Fetuin-A concentrations. **Results:** Prediabetic participants exhibited significantly higher mean serum Fetuin-A levels compared to apparently healthy subjects (439.62 ± 176.44 vs. 202.52 ± 115.12 ng/mL, $p<0.001$). Fetuin-A was positively correlated with FBG, OGTT, HbA1c, systolic blood pressure, and body mass index, while no significant correlations ($p>0.05$) were found with other biochemical or lifestyle parameters. **Conclusion:** Elevated serum levels of Fetuin-A are strongly related to prediabetes and multiple metabolic risk indicators. These findings support Fetuin-A as a probable preliminary biomarker for recognizing individuals at increased risk of diabetes. To fully confirm these findings, suggest that more extensive, larger-scale studies would be beneficial.

Keywords: *Biomarker; Duhok City; Fetuin-A; Insulin Resistance; Metabolic Risk; Prediabetes*

Introduction

The term prediabetes was introduced by the American Diabetes Association (ADA) to identify the individuals whose blood glucose levels are above the normal range but do not qualify them as having type 2 diabetes mellitus (T2DM) (Kim, 2024). The condition is characterized by a number of important indicators, such as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and high levels of glycated hemoglobin (HbA1c) levels, none of which has been deemed sufficient to cause a diabetes diagnosis (Sibiya *et al.*, 2024).

Insulin resistance (IR) plays a central role in the pathogenesis of prediabetes. Reduced insulin sensitivity impairs glucose uptake and utilization in peripheral tissues, leading to hyperglycemia, elevated triglyceride levels, and disruption of overall glucose homeostasis (Ping *et al.*, 2024). Consequently, patients with prediabetes are found to have a significantly high risk of developing T2DM and developing cardiovascular and metabolic complications (Suleiman *et al.*, 2023).

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Globally, the prediabetes rates have been increasing to concerning levels, representing a major public health challenge, particularly in developing countries such as Iraq. In 2025, the International Diabetes Federation estimates that roughly 12.0% of adults, or 634.8 million people worldwide, have IGT, and this number is projected to increase to 647.5 million adults by 2025.

Fetuin-A (Fet-A), or alpha-2-HeremansSchmid glycoprotein (AHSG) is a glycoprotein, which is mainly produced by the liver, with a smaller production in adipose tissue, making it both a hepatokine and an adipokine (Abebe *et al.,* 2022). Fet-A modulates insulin receptor signaling and inflammatory pathways and has been linked to the development of metabolic disorder, including T2DM, cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome (PCOS) (Icer *et al*., 2025). Elevated Fet-A concentrations associated with obesity indices, hyperglycemia, and IR (Zhang *et al*., 2020; Ren *et al*., 2020).

Given these associations, the present study aimed to evaluate levels of serum Fet-A and their association with IR in individuals with prediabetes in Duhok City. Based on what it know so far, this is initial study addressing its kind in this region.

Materials and Methods

Our study was a cross-sectional study, and it was conducted in the city of Duhok, Kurdistan Region of Iraq, between September 1st, 2024, and July 1st, 2025. Our study included 150 individuals, all of whom were between 18 to 75 years old, comprising 75 prediabetic individuals and 75 Apparently Healthy subjects. Participants were recruited from Azadi Teaching Hospital and the Central Public Health Laboratory using a convenience non-random sampling method during routine health check-ups.

Prediabetes was diagnosed according to American Diabetes Association (ADA) criteria: fasting plasma glucose (FPG) levels between 100 and 125 mg/dL and glycated hemoglobin (HbA1c) levels between 5.7% and 6.4%. All participants fasted for 12–14 hours prior to venous blood collection. 10 milliliters fasting blood sample was obtained from the antecubital vein, followed by the administration of a 75 g oral glucose load. A second blood sample was collected exactly two hours later for the oral glucose tolerance test (OGTT). Of the fasting sample, 7 milliliters were collected into a serum separator tube containing clot activators.

Biochemical analyses included measurements of FPG and 2-hour OGTT by using Enzymatic reference method with hexokinase, fasting serum insulin by using sandwich electrochemiluminescence immunoassay (ECLIA), and HbA1c by Turbidimetric Inhibition Immunoassay (TINIA) using a Cobas 6000 analyzer (Roche Diagnostics, Germany). IR was determined by using Homeostasis Mode1 Assessment formula:

HOMA-IR=Fasting glucose (mg/dL) * Fasting insulin (mIU/mL)/405

Serum Fetuin-A concentration was assessed quantitatively by using Enzyme-Linked Immunosorbent Assay (ELISA). Kit manufacturer company: (Reed Biotech Ltd) Catalog NO.: RE1211H.

Ethical Approval

The protocol used in the study was ethically approved by both the Scientific Committee of the Duhok Polytechnic University, College of Health and Medical Techniques and the Ethical Committee of the General Directorate of Health in Duhok Governorate, Directorate of Planning with reference number 31072024-6-34, July 31st July 2024.

Statistical Analysis

The Statistical Package of the Social Sciences (SPSS, Version 26) was used in the statistical analysis. The continuity variables were represented in descriptive statistics as mean, SD, frequencies and percentages (%) as a frequency and percentage respectively. The independent samples t-test or Pearson chi-square test was used to assess group differences between prediabetic and control cohorts with regard to general and biochemical parameters. It was determined that bivariate correlation analyses were conducted to determine the relationships among serum Fet-A levels and

other biochemical variables among the prediabetic sample. The statistical significance was determined as less than 0.05 or $p<0.05$.

Results

Compares the proportion in each group presented in Table 1. The mean age of prediabetic individuals (46.41 years) was like that of Apparently healthy subjects. However, both BMI and WC were higher among prediabetic participants compared with Apparently healthy subjects ($p<0.001$), indicating a predominance of obesity within the prediabetic group.

Moreover, prediabetic individuals exhibited elevated diastolic and systolic blood pressure mean compared with apparently healthy subjects (both $p<0.001$). A greater proportion of prediabetic subjects reported as positive family history of diabetes and cardiovascular diseases (CVDs) and were more likely to be physically inactive compared with the healthy group.

Table 1: *Comparison The Proportion of Subjects in Each Group*

Variables		Prediabetics subjects (N=75)	Apparently Healthy subjects (N=75)	*p*-value
Age (years)		46.41±11.79	46.11±12.26	0.876
Waist circumference (CM)		105.17±15.62	97.87±17.03	0.007
BMI (kg/m2)		32.29±5.81	28.26±5.16	<0.001
SBP (mmHg)		128.40±13.09	120.41±11.35	<0.001
DBP (mmHg)		84.27±7.95	78.81±8.46	<0.001
Gender	Male	35(46.7%)	37(49.3%)	0.435
	Female	40(53.3%)	38(50.7%)	
Family history of Diabetes	Positive	41(54.7%)	25(33.3%)	0.007
	Negative	34(45.3%)	50(66.7%)	
Family history of cardiovascular disease	Positive	44(58.7%)	29(38.7%)	0.011
	Negative	31(41.3%)	46(61.3%)	
History of cardiovascular disease	Positive	9(12%)	0	0.002
	Negative	66(88%)	75(100%)	
History of medication	Yes	14(18.7%)	0	<0.001
	No	61(81.3%)	75(100%)	
Smoking habits	Yes	39(52%)	27(36%)	0.035
	No	36(48%)	48(64%)	
Physical Activity	Yes	17(22.7%)	35(46.7%)	0.002
	No	58(77.3%)	40(53.3%)	

Table 2: *Prediabetics and Subjects' Biochemical Parameters According to Study Group*

Variables	Prediabetics subjects (N=75)	Apparently Healthy subjects (N=75)	*P*-value
Fasting blood glucose (mg/dL)	107.83±8.21	89.56±6.09	<0.001
< 100	7 (9.3%)	75 (100%)	
100 to 125	68 (90.7%)	0	<0.001
2h-OGT mg/dL	147.55±24.74	104.71±15.79	<0.001
< 140	23 (30.7%)	75 (100%)	
140 to 199	52 (69.3%)	0	<0.001
HbA1c %	5.76±0.45	4.99±0.49	<0.001
<5.7 %	24 (32%)	70 (93.3%)	
57-6.4 %	51 (68%)	5 (6.7%)	<0.001
Fasting Insulin levels (mIU / mL)	15.94±8.14	10.00±4.87	<0.001
2.6 to 24.9	67 (89.3%)	74 (98.7%)	
≥ 25	8 (10.7%)	1 (1.3%)	0.017
HOMA-IR	4.24±2.23	2.21±1.09	<0.001
<3.0	20 (26.7%)	60 (80%)	
≥3.0	55 (73.3%)	15 (20%)	<0.001
Fetuin-A (ng/mL)	439.62±176.44	202.52±115.12	<0.001

The biochemical parameters of study participants are displayed in Table 2. Prediabetic individuals exhibited a higher serum Fetuin-A levels compared with healthy controls (439.62 ± 176.44 ng/mL vs. 202.52 ± 115.12 ng/mL, p <0.001). In addition, prediabetic participants demonstrated significantly

elevated levels of FBS, 2h-OGT, HbA1c, HOMA-IR and insulin level are compared with apparently healthy subjects (all $p<0.001$), indicating marked metabolic dysregulation.

The associations between serum Fetuin-A concentrations and demographic and clinical characteristics among prediabetic participants (N = 75) are presented in Table 3. Concentration of serum Fet-A was slightly greater in subjects with IFG compared to IGF or both IGT and IFG subjects; however, these differences were not statistically significant. A significant relationship was identified between Fetuin-A concentration, blood pressure (systolic) and BMI, with greater Fetuin-A levels in participants with normal BMI and lower systolic pressure compared with overweight, obese, and hypertensive individuals ($p<0.05$). No associations were found between Fetuin-A and other variables ($p>0.05$), including age, gender, waist circumference, or family history of diabetes.

Table 3 : *Association of Fetuin-Awith Participant Characteristics in Prediabetics*

Variables		Fetuin-A in Prediabetics subjects (N= 75)		
		N (%)	Mean ±SD	*p*-value
Statues	IFG	23 (15.3%)	464.01±179.72	0.057
	IGT	7 (4.7%)	289.93±68.49	
	IGF and IGT	45 (30%)	450.43±177.68	
Sex	Male	35 (46.7%)	411.27±135.16	0.195
	Female	40 (53.3%)	464.42±204.43	
Age (years)	18-30 years	7 (9.3%)	461.03±204.64	0.501
	31-50 years	38 (50.7%)	458.5±179.54	
	51-70 years	29 (38.7%)	416.87±167.42	
	≥71 years	1 (1.3%)	232.14	
Waist circumference (CM)	Male <102 CM ≥102 CM	 11 (14.7%) 24 (32%)	 397.54±154.77 417.57±128.29	0.690
	Female <88 CM ≥88 CM	 6 (8%) 34 (45.3%)	 492.29±200.98 459.50±207.64	0.722
BMI (kg/m2)	Normal 18.5 - 24.9	4 (5.3%)	575.45±174.04	0.046
	Overweight 25 - 29.9	26 (34.7%)	379.96±165.97	
	Obese ≥30	45 (60%)	462.01±174.21	
SBP (mmHg)	<130 mmHg	36 (48%)	489.18±180.19	0.018
	≥130 mmHg	39 (52%)	393.87±162.00	
DBP (mmHg)	<85 mmHg	35 (46.7%)	443.64±190.28	0.855
	≥85 mmHg	40 (53.3%)	436.10±165.76	
Family history of Diabetes	Positive	41 (54.7%)	408.43±166.73	0.093
	Negative	34 (45.3%)	477.24±182.89	
Family history of cardiovascular disease	Positive	44 (58.7%)	455.75±176.02	0.349
	Negative	31(41.3%)	416.72±177.36	
History of cardiovascular disease	Positive	9 (12%)	329.92±199.33	0.401
	Negative	66 (88%)	445.99±173.81	
History of medication	Yes	14 (18.7%)	425.34±234.32	0.740
	No	61 (81.3%)	442.89±162.60	
Smoking habits	Yes	39 (52%)	457.34±177.63	0.369
	No	36 (48%)	420.42±175.60	
Physical Activity	Yes	17 (22.7%)	475.52±191.35	0.343
	No	58 (77.3%)	429.09±172.16	

The association of biochemical parameters with Fetuin-A levels in prediabetic subjects is represented in Table 4. A meaningful relationship was found between serum Fet-A levels and glycemic markers, including FBS, 2h-OGT and HbA1c ($p<0.05$). Conversely, no significant relations were found between Fetuin-A, Fasting insulin levels and HOMA-IR.

Table 4 : *Association of Biochemical Parameters With Fetuin-A İn Prediabetics*

Parameters		Fetuin-A in Prediabetics subjects (N= 75)		
		N (%)	Mean ±SD	*p*-value
Fasting blood glucose (mg/dL)	< 100	25 (33.3%)	481.65±155.66	0.020
	100 to 125	50 (66.7%)	393.91±147.61	
2h-OGT (mg/dL)	< 140	40 (53.3%)	465.69±163.73	0.010
	140 to 199	35 (46.7%)	374.46±130.24	
HbA1c (%)	<5.7 %	44 (58.7%)	455.84±162.70	0.028
	57-6.4 %	31 (41.3%)	376.66±132.32	
Fasting Insulin levels (mIU / mL)	2.6 to 24.9	72 (96%)	430.11±154.17	0.055
	≥25	3 (4%)	255.09±30.21	
HOMA-IR	<3.0	31 (41.3%)	454.29±154.06	0.145
	≥3.0	44 (58.7%)	401.15±153.57	

The study conducted a Pearson correlation analysis to examine associations between Fetuin-A concentrations and biochemical as well as demographic parameters in 75 prediabetic individuals (Table 5). Among the variables analyzed, only fasting blood sugar (FBS) showed a statistically positive correlation with Fetuin-A (r=0.282, *p*=0.014), indicating that greater Fetuin-A concentrations are correlated with elevated FBS. No correlations were observed between Fetuin-A and other glycaemic parameters, including 2-hour OGTT, HbA1c, fasting insulin levels, or HOMA-IR, waist circumference, BMI, or blood pressure, with most *p*-values exceeding 0.05.

Table 5: *Correlations of Fetuin-AWith Biochemical Markers and General Characteristics in Prediabetics*

Parameters	Fetuin A,Prediabetics Subjects (N= 75)	
	Pearson Correlation (R)	Sig.(2-Tailed)
Fasting blood glucose (mg/dL)	0.282	**0.014**
2h-OGT (mg/dL)	0.041	0.724
HbA1c (%)	-0.130	0.265
Fasting Insulin levels (mIU / mL)	-0.169	0.148
HOMA-IR	-0.125	0.284
Sex	0.151	0.195
Age (years)	-0.178	0.126
Waist circumference (CM)	-0.092	0.432
BMI (kg/m2)	0.059	0.613
SBP (mmHg)	-0.121	0.300
DBP (mmHg)	-0.042	0.719

A significant positive correlation was seen between serum Fet-A levels, FBS in prediabetic individuals, as shown in the simple scatter plot in Figure 1. Demonstrating a strong linear correlation whereby an increase in FBS levels corresponds with a rise in Fetui-A levels.The Y-axis represents Fetuin-A while X-axis represent FBS.

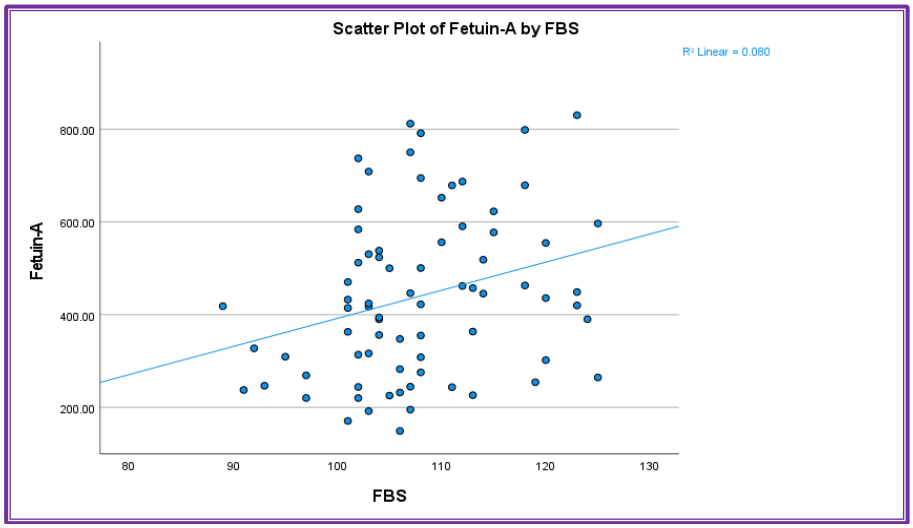


Figure 1: *Serum Fetuin-A And FBS Correlation in Prediabetics Individuals.*

The area under the curve ROC curve was 0.875 (95% CI: 0.822-0.928), indicating excellent discriminatory power of serum Fetuin-A for differentiating prediabetes from controls. The optimal cut-off was 151.455 ng/ml, yielding a sensitivity of a 98.7% & specificity of 60%. The ROC analysis was statistically significant (p<0.001) as shown in Table 6, Figure 2.

Table 6: *ROC Curve Analysis of Serum Fetuin-A In Study Population*

Test Variable	Area Under Curve	95% CI	Cut-off point(ng/ml)	Sensitivity (%)	Specificity (%)	*p* value
Fetuin-A(ng/ml)	0.875	0.822 - 0.928	151.455	98.7	60.0	<0.001

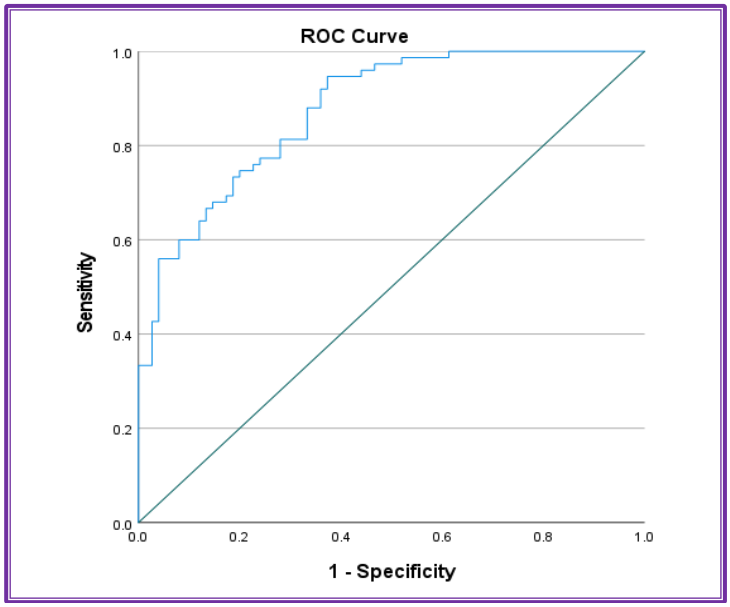


Figure 2: *ROC Curve Analysis of Serum Fetuin*

The overall regression model was not statistically significant, F (3, N–4) = 1.083, p = 0.362, indicating that the predictors jointly do not explain a significant proportion of variance in the outcome variable. The model explains approximately 4.4% (R^2 = 0.044) of the variance, and the adjusted R^2 of 0.003 suggests that the model has minimal explanatory power after adjusting for the number of predictors as presented in Table 7.

Table 7: *Multiple Regression Analysis of Fetuin-A Levels Adjusted for Age, BMI, and Gender in Prediabetic Participants*

Variable	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	SE	Beta		
Constant	44.601	154.481		2.897	0.005
Age	32.728	44.279	0.093	0.739	0.462
BMI	-2.256	1.849	-0.151	-1.220	0.226
Gender	1.441	3.632	0.047	0.937	0.693
Model Summary: R= 0.209[a] R^2 = 0.044 Adjusted R^2 = 0.003 F-statistic = 1.083 p-value= 0.362					

Discussion

Prediabetes is a prevalent metabolic condition, having an impact on nearly 1/3 to half of the global population, and it is linked to increased risk of CVD development (Echouffo-Tcheugui & Selvin, 2021; Rooney *et al*., 2023). In the current study, prediabetic participants exhibited significantly higher BMI, waist circumference and blood pressure, significant alterations in key metabolic parameters, including

FBS, 2h-OGT, HbA1c, insulin, HOMA-IR, and serum Fetuin-A concentrations, consistent with prior research highlighting complex metabolic dysregulation in prediabetes.

Anthropometric analyses revealed that prediabetic individuals had significantly higher BMI and waist circumference compared to healthy controls, corroborating previous studies in Duhok City (Abdullah & Salih, 2023; Suleiman *et al*., 2023) and supporting central obesity as a critical factor in insulin resistance and T2DM pathogenesis (Liu *et al*., 2023). Elevated systolic and diastolic blood pressures were also observed among prediabetics, aligning with meta-analytic evidence linking hypertension to progression from prediabetes to cardiovascular diseases and diabetes (Sattar *et al*., 2024).

Concentrations of Fet-A were significantly higher in prediabetic participants (439.62 ± 176.44 ng/mL) compared to controls (202.52 ± 115.12 ng/mL, $p<0.001$), supporting its role as a hepatokine involved in Metabolic syndrome and IR. Fet-A is known to inhibit insulin receptor tyrosine kinase activity, impairing peripheral glucose uptake and insulin signaling (Karamfilova *et al*., 2023). Statistically significant correlations were observed between Fetuin-A and glycemic markers, particularly FBS, 2h-OGTT, and HbA1c, consistent with previous studies indicating its association with early glucose dysregulation (Karamfilova *et al*., 2023).

Interestingly, no statistically significant relations were observed between Fet-A and HOMA-IR, fasting insulin levels, BMI, waist circumference, or lifestyle factors such as physical activity and smoking, suggesting that the regulation of Fet-A is likely multifactorial, produced mainly by the liver and is influenced more by hepatic steatosis, low grade inflammation, insulin resistance, and genetic factors than by BMI alone (Lee-Ødegård *et al*., 2022). Notably Fet-A concentrations were unexpectedly grater in participants with normal BMI and lower systolic blood pressure, possibly reflecting early-phase metabolic dysregulation prior to overt obesity or hypertension (Icer *et al*., 2025). Thus, some lean individuals can be metabolically unhealthy (higher visceral fat or NAFLD) and exhibit elevated Fetuin-A despite normal BMI and normotension (Liu *et al*., 2020).

Having a family history of diabetes was significantly linked to prediabetes, highlighting the contribution of genetic and environmental factors, though no direct association with Fetuin-A levels was observed. Similarly, family history of CVD and personal history of CVD were more common in prediabetic subjects but did not correlate significantly with Fetuin-A, likely due to sample size limitations (Cai *et al*., 2020).

Overall, our findings highlight the utility of Fetuin-A as a potential early biomarker for prediabetes and impaired glucose regulation, while also highlighting the importance of anthropometric, glycemic, and familial risk factors in assessing metabolic and cardiovascular risk. Further, longitudinal studies involving larger and more diverse populations are essential to clarify the mechanisms linking Fetuin-A with prediabetes and related comorbidities.

Conclusion

In conclusion, this thesis has demonstrated that significantly elevated serum Fetuin-A in prediabetic individuals compared to the healthy control was found. Collectively, Hight levels of Fetuin-A, abnormal biochemical parameters and abnormally high atherogenic indices among prediabetes individuals will exacerbate the chance of developing diabetes. This result supports the hypothesis of the important role of serum Fet-A in the development and progression of glucose intolerance and insulin resistance. Therefore, early diagnosis and management of prediabetes are crucial, as the higher levels of Fet-A are linked to prediabetes, thus decreasing the development risk of diabetes.

Recommendations

The following recommendations are proposed:

1. **Increase Diversity and Sample Size:** Future studies should recruit more and larger demographically diverse populations to enhance the generalizability and external validity of the results across different age groups, genders, and regional populations.

2. **Employ Case-Control Study Designs:** Utilizing a case-control design would allow better control of potential confounding factors affecting the relationship between Fetuin-A and prediabetes, facilitating more robust comparisons between prediabetic and control groups.
3. **Detailed Assessment of Lifestyle Factors:** To clarify the interactions between metabolic health and Fetuin-A, future research should incorporate comprehensive evaluations of lifestyle variables, including stress levels, sleep quality, dietary patterns, and physical activity intensity.

These measures will help to deepen understanding of the role of Fetuin-A in prediabetes and its capability as an early biomarker for metabolic dysfunction.

Conflict of Interest

No conflicts of interest.

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