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ORIGINAL RESEARCH

EXPLORING FETUIN-A AS A POTENTIAL BIOMARKER FOR TYPE 2 DIABETES MELLITUS: A CASE-CONTROL STUDY

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ABSTRACT

Background: This study aimed to investigate the association between various blood parameters and diabetic status, with a particular focus on Fetuin-A levels as a potential biomarker.

Methods: A cross-sectional case-control study was conducted among 140 participants, comprising 70 cases with type 2 diabetes mellitus and 70 controls. Anthropometric measurements, blood pressure, fasting and postprandial blood glucose levels, lipid profiles, and serum Fetuin-A levels were assessed using standard techniques.

Results: Significant differences were observed between cases and controls for various parameters: fasting blood sugar (136.3 mg/dL vs. 84.6 mg/dL, $p < 0.0001$), postprandial blood sugar (218 mg/dL vs. 121.3 mg/dL, $p < 0.0001$), total cholesterol (194 mg/dL vs. 170 mg/dL, $p < 0.0001$), triglycerides (143 mg/dL vs. 119 mg/dL, $p < 0.0001$), HDL (49 mg/dL vs. 58 mg/dL, $p < 0.0001$), LDL (115 mg/dL vs. 87.4 mg/dL, $p < 0.0001$), systolic blood pressure (120 mm Hg vs. 109 mm Hg, $p < 0.0001$), diastolic blood pressure (80 mm Hg vs. 73.9 mm Hg, $p < 0.0001$), and Fetuin-A levels (11.6 ng/mL vs. 3.5 ng/mL, $p < 0.0001$).

Conclusion: Our findings suggest a significant association between blood parameters and diabetic status, with Fetuin-A emerging as a potential biomarker for risk stratification. Further research is warranted to explore its clinical utility in diabetes management.

Keywords: Diabetes Mellitus, Type 2; Biomarkers; Blood Glucose; Lipid Profile; Fetuin-A; Case-Control Studies

INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder characterized by elevated blood glucose levels, poses a significant global health challenge.[1] With an escalating prevalence worldwide, diabetes imposes a substantial burden on individuals, healthcare systems, and economies. Among its various forms, type 2 diabetes mellitus (T2DM) constitutes most diabetes cases, representing a multifactorial disease with complex pathophysiology.[2]

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In recent decades, extensive research has focused on elucidating the intricate mechanisms underlying the development and progression of T2DM. While insulin resistance and impaired insulin secretion are well-established hallmarks of the disease, emerging evidence suggests the involvement of additional factors, including adipokines, cytokines, and hepatokines, in the intricate interplay of metabolic dysregulation.[3]

Fetuin-A, a multifunctional glycoprotein primarily synthesized in the liver, has garnered increasing attention for its potential role in glucose homeostasis and insulin sensitivity.[4] Initially identified as a potent inhibitor of vascular calcification, Fetuin-A has since been implicated in various physiological processes, including inflammation, insulin signaling, and lipid metabolism.[5]

The association between Fetuin-A and T2DM has attracted considerable interest, driven by compelling preclinical and clinical data suggesting a possible link between altered Fetuin-A levels and insulin resistance.[6] Experimental studies in animal models and in vitro cell cultures have demonstrated that Fetuin-A can modulate insulin signaling pathways, contributing to impaired insulin sensitivity and glucose intolerance. Moreover, epidemiological investigations have revealed an inverse correlation between circulating Fetuin-A concentrations and insulin sensitivity in both healthy individuals and patients with T2DM.[5, 6]

Furthermore, several studies have highlighted the potential utility of Fetuin-A as a predictive biomarker for the development of T2DM and its associated complications.[7, 8] Elevated serum Fetuin-A levels have been associated with an increased risk of incident T2DM, independent of traditional risk factors such as obesity and dyslipidemia. Moreover, longitudinal studies have demonstrated that higher baseline Fetuin-A levels predict a greater decline in insulin sensitivity over time, underscoring its potential prognostic significance in T2DM progression.[9]

Despite these intriguing findings, the precise mechanisms underlying the relationship between Fetuin-A and T2DM remain incompletely understood. Moreover, conflicting results have been reported regarding the association between Fetuin-A levels and various metabolic parameters, including fasting plasma glucose (FPG) and serum triglyceride levels.[10] While some studies have reported positive correlations between Fetuin-A and FPG or triglycerides, others have failed to confirm such associations, suggesting potential heterogeneity in study populations or methodological differences.[11]

Considering these uncertainties, further research is warranted to elucidate the role of Fetuin-A in T2DM pathogenesis and its potential implications for clinical practice. Accordingly, the present observational study seeks to investigate the association between serum Fetuin-A levels and T2DM in a cohort of patients with established T2DM and age-matched healthy controls. Additionally, we aim to explore the correlations between Fetuin-A levels and key metabolic parameters, including FPG and serum triglycerides, to provide insights into the underlying mechanisms linking Fetuin-A to T2DM and its metabolic sequelae.

By addressing these objectives, our study endeavors to contribute to the growing body of literature on the role of Fetuin-A in T2DM and its potential utility as a biomarker for risk stratification and therapeutic targeting. Ultimately, a deeper understanding of the complex interplay between Fetuin-A and T2DM may pave the way for novel diagnostic and therapeutic strategies aimed at mitigating the burden of this prevalent and debilitating disease.

MATERIALS & METHOD

Study Setting: The present study employed a Cross-Sectional Case-Control design and was conducted at the Department of Biochemistry, Thanjavur Medical College, Thanjavur. The study spanned over a period of one year.

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Study Participants: Participants for the study were recruited from two departments: the Department of Internal Medicine's Outpatient Department (OPD) and the Department of Diabetology. The inclusion criteria encompassed patients diagnosed with Type 2 Diabetes Mellitus, aged over 25 years, regardless of gender. Exclusion criteria included individuals with malignancy, liver disease, kidney disease, or blood disorders.

Sample Size: The sample size calculation was based on the International Diabetes Federation (IDF) 2020 report, indicating a diabetes prevalence of 8.9%. With a desired power of 80%, absolute precision of 5%, and a confidence interval of 95%, the calculated sample size was 140 (70 cases and 70 controls).

Sampling Technique: Convenience sampling was employed to recruit participants meeting the inclusion criteria from the designated departments during the study period.

Study Methodology: Upon obtaining informed consent from all participants, baseline parameters such as blood pressure and anthropometric data (height, weight) were measured using standardized techniques. Blood samples were collected into serum separator tubes, allowed to clot for 2 hours at room temperature, and then centrifuged at 1000 × g for 20 minutes. The resulting serum samples were stored in aliquots at -20°C until further analysis.

Study Tools: Anthropometric measurements, including height and weight, were obtained using calibrated instruments. Body Mass Index (BMI) was calculated using the standard formula. Blood pressure was measured using a Mercury Sphygmomanometer, with the higher of the two readings considered for classification if systolic and diastolic pressures differed.

Biochemical investigations were conducted using a Beckmann Coulter fully automated machine. Parameters analyzed included Fasting Blood Glucose, Serum Fetuin-A, and Lipid Profile components (Total Cholesterol, HDL, LDL, Triglycerides).

1. **Estimation of Plasma Glucose (GOD-POD method):** The glucose oxidase (GOD) - peroxidase (POD) method is based on the enzymatic oxidation of glucose-by-glucose oxidase to produce gluconic acid and hydrogen peroxide. The hydrogen peroxide then reacts with phenolic compound and 4-aminoantipyrine in the presence of peroxidase to form a colored quinonimine complex, the intensity of which is directly proportional to the glucose concentration in the sample. A small volume of plasma (10 µl) is added to an enzyme reagent containing phosphate buffer, glucose oxidase, peroxidase, 4-aminoantipyrine, and phenol. The mixture is incubated for 10 minutes at 37°C. After incubation, the absorbance of the sample is measured at 505nm using a spectrophotometer. The concentration of glucose in the sample is determined by comparing its absorbance to that of a standard curve generated using known concentrations of glucose.
2. **Estimation of Serum Fetuin-A (ELISA method):** The Enzyme-Linked Immunosorbent Assay (ELISA) is a highly sensitive method used to quantify the concentration of a specific protein in a sample. In the sandwich ELISA technique used for Fetuin-A estimation, a microplate is pre-coated with an antibody specific to Fetuin-A. Samples or standards containing Fetuin-A are added to the wells, followed by the addition of a biotinylated antibody specific to Fetuin-A. After incubation and washing steps to remove unbound substances, a streptavidin-horseradish peroxidase (HRP) conjugate is added, which binds to the biotinylated antibody. Addition of a substrate solution results in a color change, the intensity of which is proportional to the amount of Fetuin-A present in the sample. The absorbance is measured at a specific wavelength using a spectrophotometer.
3. **Estimation of Serum Total Cholesterol (Cholesterol oxidase - Peroxidase method):** The Cholesterol oxidase - Peroxidase method relies on the enzymatic oxidation of cholesterol-by-cholesterol oxidase to produce cholestenone and hydrogen peroxide. The hydrogen peroxide

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then reacts with a phenolic compound and 4-aminoantipyrine in the presence of peroxidase to form a colored quinonimine complex. The intensity of the color is directly proportional to the cholesterol concentration in the sample. A small volume of serum (10 µl) is added to an enzyme reagent containing cholesterol oxidase, cholesterol esterase, peroxidase, 4-aminoantipyrine, and phenol. The mixture is incubated for 10 minutes at 37°C. After incubation, the absorbance of the sample is measured at 505nm using a spectrophotometer. The concentration of cholesterol in the sample is determined by comparing its absorbance to that of a standard curve generated using known concentrations of cholesterol.

4. **Estimation of Serum Triglycerides (GPO-PAP method):** The Glycerol Phosphate Oxidase - Peroxidase (GPO-PAP) method involves the enzymatic hydrolysis of triglycerides by lipoprotein lipase to release glycerol, which is phosphorylated by glycerol kinase to form glycerol-3-phosphate. Glycerol-3-phosphate is oxidized by glycerol phosphate oxidase to produce dihydroxyacetone phosphate and hydrogen peroxide. The hydrogen peroxide then reacts with a chromogenic substance in the presence of peroxidase to form a colored complex, the intensity of which is directly proportional to the triglyceride concentration in the sample. A small volume of serum (10 µl) is added to an enzyme reagent containing glycerol phosphate oxidase, lipoprotein lipase, glycerol kinase, peroxidase, and a chromogenic substance. The mixture is incubated for 10 minutes at 37°C. After incubation, the absorbance of the sample is measured at 505nm using a spectrophotometer. The concentration of triglycerides in the sample is determined by comparing its absorbance to that of a standard curve generated using known concentrations of triglycerides.
5. **Estimation of Serum HDL-Cholesterol (Direct method):** The Direct method for HDL-Cholesterol estimation involves the selective reaction of HDL with specific detergents and enzymes to produce hydrogen peroxide. The hydrogen peroxide then reacts with a chromogenic substance in the presence of peroxidase to form a colored complex, the intensity of which is directly proportional to the HDL-Cholesterol concentration in the sample. A small volume of serum (2 µl) is added to enzyme reagents containing detergents, cholesterol esterase, cholesterol oxidase, peroxidase, and a chromogenic substance. The mixture is incubated for 10 minutes at 37°C. After incubation, the absorbance of the sample is measured at 600nm using a spectrophotometer. The concentration of HDL-Cholesterol in the sample is determined by comparing its absorbance to that of a standard curve generated using known concentrations of HDL-Cholesterol.

Statistical Analysis: Statistical analysis was performed using IBM SPSS software version 25. Appropriate methods to determine associations between serum Fetuin-A levels and T2DM, as well as correlations with Fasting Plasma Glucose and serum triglyceride levels. Descriptive statistics, such as means, standard deviations, and frequencies, were calculated. Inferential statistics, including t-tests and correlation coefficients, were utilized to assess associations and correlations.
Ethical Issues: Ethical clearance for the study was obtained from the institutional ethics committee. Informed consent was obtained from all participants prior to their inclusion in the study. Confidentiality and privacy of participant data were strictly maintained throughout the study process. All procedures were conducted in accordance with ethical standards and guidelines.

RESULTS

The study reveals significant differences in age between the control and study groups, with the mean age of participants in the study group (49.7 years) being notably higher than that of the control group (44.1 years), demonstrating statistical significance ($t = 2.53$, $df = 138$, $p = 0.012$). Regarding gender distribution, both groups exhibited similar proportions of males and females,

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with no statistically significant difference observed ($\chi^2 = 0.457$, df = 1, p = 0.612). Furthermore, there were no significant disparities in anthropometric measurements such as weight (t = 0.38, df = 138, p = 0.699), height (t = 1.93, df = 138, p = 0.055), and BMI (t = 1.37, df = 138, p = 0.171) between the control and study groups. Overall, while age differed significantly between the groups, there were no notable distinctions in gender distribution or anthropometric characteristics among the study population.

Table 1: Comparison of blood parameters between cases and controls

S.No	Parameters	Controls (N=70)		Study group (n=70)		t value	P value
		Mean	SD	Mean	SD		
1	FBS (mg/dL)	84.6	7.9	136.3	18.3	21.5	<0.0001*
2	PPBS (mg/dL)	121.3	9.2	218	39.1	20.1	<0.0001*
3	Total cholesterol (mg/dL)	170	16.9	194	27.5	5.9	<0.0001*
4	Triglycerides (mg/dL)	119	17.4	143	14.6	9.1	<0.0001*
5	HDL (mg/dL)	58	9.9	49	9.9	5.1	<0.0001*
6	LDL (mg/dL)	87.4	9.8	115	17.5	11.5	<0.0001*
7	SBP (mm Hg)	109	7.2	120	15.1	5.6	<0.0001*
8	DBP (mm Hg)	73.9	4.2	80	8.3	5.4	<0.0001*
9	Fetuin-A (ng/ml)	3.5	2.2	11.6	5.4	11.7	<0.0001*

Table 1 reveals significant differences in various blood parameters between the study group and the control group. Parameters such as fasting blood sugar (FBS), postprandial blood sugar (PPBS), total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), systolic blood pressure (SBP), diastolic blood pressure (DBP), and Fetuin-A levels exhibited statistically significant differences ($p < 0.0001$*) between the two groups.

Table 2. Correlation of various parameters with respect to Fetuin-A (ng/ml) levels in the study population.

S.No	Correlation of Fetuin-A level	Study group		Control group	
		Pearson's R	P value	Pearson's r	P value
1	DBP (mm Hg)	0.320	0.007*	-0.210	0.08 (NS)
2	SBP	0.201	0.095 (NS)	-0.251	0.036*
3	Total Cholesterol (mg/dL)	-0.059	0.631 (NS)	-0.158	0.191 (NS)
4	Triglycerides (mg/dL)	-0.152	0.208 (NS)	-0.078	0.519 (NS)
5	HDL (mg/dL)	0.125	0.303 (NS)	0.026	0.834 (NS)
6	LDL (mg/dL)	0.056	0.647 (NS)	0.201	0.095 (NS)
7	BMI	0.004	0.972 (NS)	0.056	0.647 (NS)

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8	FBS (mg/dL)	-0.193	0.109 (NS)	-0.139	0.251 (NS)
9	PPBS (mg/dL)	-0.144	0.236 (NS)	-0.044	0.720 (NS)

Furthermore, Table 2 illustrates the correlation of Fetuin-A levels with different parameters in both study and control groups, indicating significant correlations ($p < 0.05$) with DBP and SBP in the study group. Additionally, Table 3 showcases the receiver operating characteristic (ROC) characteristics of FBS, PPBS, and Fetuin-A in predicting diabetic status, revealing high area under the curve (AUC) values for FBS (0.998) and PPBS (1), and a slightly lower AUC value for Fetuin-A (0.933), all with significant p values ($p < 0.0001$). Figure 1 visually represents the ROC curves of these parameters.

Table 3. ROC characteristics of fetuin-A in predicting the diabetic status observed in the study

S.No	Parameter	N	Area under curve	Std error	P value
1	FBS (mg/dL)	140	0.998	0.002	<0.0001*
2	PPBS (mg/dL)	140	1	0.0001	<0.0001*
3	Fetuin-A	140	0.933	0.019	<0.0001*

Moreover, Table 4 presents the diagnostic indices for predicting prediabetic and diabetic status by various parameters, indicating high sensitivity and specificity values for FBS and PPBS in diagnosing both prediabetes and diabetes, while Fetuin-A demonstrates moderate sensitivity and specificity for prediabetes.

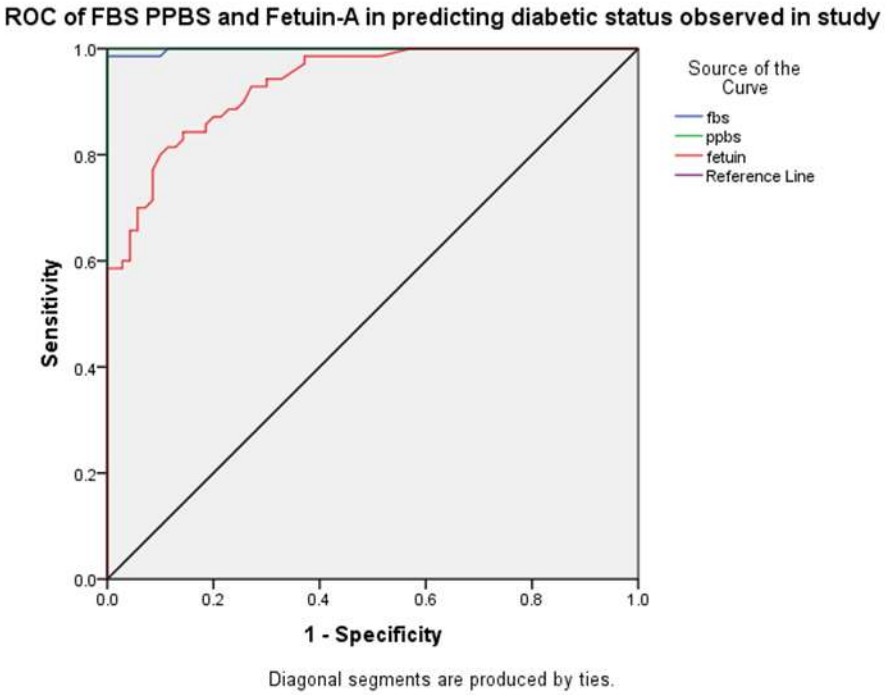

Figure 1: ROC of FBS, PPBS, and Fetuin-A in predicting diabetic status

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Table 4. Diagnostic indices of predicting the prediabetic status by various parameters observed in the study (n=140).

Parameter		Cut off value	Sensitivity	Specificity
Prediabetes status	FBS (mg/dL)	>100	98.6%	100%
	PPBS (mg/dL)	>140	100%	100%
	Fetuin-A (ng/ml)	>4.25	90%	75%
Diabetes status	FBS (mg/dL)	>126	75%	100%
	PPBS (mg/dL)	>200	67%	100%
	Fetuin-A	>4.25	90%	75%

DISCUSSION

The present study aimed to investigate the association between various blood parameters, including fasting and postprandial blood sugar, lipid profiles, blood pressure, and Fetuin-A levels, with the diabetic status among the study population. The findings from this study provide valuable insights into the potential roles of these parameters in predicting and understanding the diabetic status, which could have significant implications for the management and prevention of diabetes mellitus.

One of the key findings of this study is the significant difference observed in fasting and postprandial blood sugar levels between the study group and the control group. This highlights the importance of monitoring and controlling blood glucose levels in individuals at risk of diabetes. Elevated levels of fasting and postprandial blood sugar have long been recognized as major risk factors for the development of diabetes and its associated complications.[12] The results of our study emphasize the importance of early detection and intervention to prevent the progression to diabetes among high-risk individuals.

Furthermore, our study also revealed significant differences in lipid profiles between the study group and the control group, including total cholesterol, triglycerides, HDL, and LDL levels. Dyslipidemia is a common comorbidity associated with diabetes and is known to contribute to the increased risk of cardiovascular diseases in diabetic individuals. The findings of our study emphasize the need for comprehensive management of lipid profiles in diabetic patients to reduce the risk of cardiovascular complications and improve overall health outcomes.[13]

Another important finding of this study is the association between blood pressure levels and diabetic status. Our results showed significantly higher systolic and diastolic blood pressure levels in the study group compared to the control group. Hypertension is a well-established risk factor for the development and progression of diabetes, and the coexistence of hypertension and diabetes further increases the risk of cardiovascular diseases and other complications. Therefore, effective management of blood pressure is essential in the prevention and management of diabetes and its associated complications.[14]

Moreover, our study investigated the role of Fetuin-A, a glycoprotein with regulatory functions in insulin signaling and glucose metabolism, in predicting diabetic status. The results demonstrated a significant elevation in Fetuin-A levels in the study group compared to the control group, and Fetuin-A levels were found to be positively correlated with blood pressure levels in the study group. These findings suggest that Fetuin-A may serve as a potential biomarker for the early detection of diabetes and its associated cardiovascular risks. Further research is warranted to elucidate the underlying mechanisms and clinical implications of Fetuin-A in diabetes pathophysiology.[15]

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The receiver operating characteristic (ROC) analysis performed in our study provided further insights into the diagnostic accuracy of various parameters in predicting diabetic status. The high area under the curve (AUC) values obtained for fasting and postprandial blood sugar levels indicate their strong predictive ability for identifying individuals at risk of diabetes. Additionally, the moderate AUC value for Fetuin-A suggests its potential utility as a complementary biomarker for diabetes risk assessment. These findings highlight the importance of incorporating multiple biomarkers into diagnostic algorithms for more accurate risk stratification and early intervention in diabetes management.[16]

Overall, the findings of this study contribute to our understanding of the complex interplay between various metabolic and cardiovascular parameters in the pathogenesis of diabetes. The identification of novel biomarkers such as Fetuin-A and the validation of traditional risk factors underscore the importance of a comprehensive approach to diabetes prevention and management. Future research should focus on elucidating the molecular mechanisms underlying the observed associations and exploring novel therapeutic targets for improving clinical outcomes in diabetic patients. Additionally, large-scale prospective studies are needed to validate the diagnostic accuracy and clinical utility of the identified biomarkers in diverse populations.

CONCLUSION

The study highlights the significant association between various blood parameters, including fasting and postprandial blood sugar, lipid profiles, blood pressure, and Fetuin-A levels, with diabetic status. These findings emphasize the importance of comprehensive metabolic and cardiovascular risk assessment in the early detection and management of diabetes. Furthermore, the identification of Fetuin-A as a potential biomarker for diabetes risk stratification warrants further investigation. Incorporating multiple biomarkers into diagnostic algorithms could improve risk prediction and facilitate early intervention strategies to mitigate the burden of diabetes and its associated complications.

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