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SERUM FETUIN-A AS AN INDEPENDENT MARKER OF INSULIN RESISTANCE IN PRE-DIABETES

Biochemistry

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ABSTRACT

BACKGROUND:- Diagnosing pre-diabetes has been a challenging task and till date it is done on the basis of levels of plasma glucose and glycated hemoglobin(HbA1c).Fetuin-Acan serve as an important marker for dianosing pre-diabetes.The present study was designed to evaluate the role of Fetuin-A levels in predicting glycaemic outcome in people with pre-diabetes.

METHODS AND MATERIALS: The present cross sectional study was carried out in Department Of Biochemistry at People's College of Medical Sciences & Research Centre, Bhopal. A total of 300 subjects were included, out of which 100 were known type 2 diabetics, 100 were pre-diabetics and 100 were normal healthy individuals. Laboratory investigations included serum fasting and 2-hour glucose, HbA1c, in sulin and Fetuin-A.Insulin resistance was calculated by Homeostatic model assesment (HOMA-IR).

RESULTS: We observed that serum Fetuin-A levels,insulin and HOMA-IR were significantly higher in known type 2 diabetics as compared to pre-diabetics and controls.

CONCLUSION: Increased Fetuin A levels had an adverse impact on glycemic outcomes in pre-diabetes thus suggesting that Fetuin A can be used as a tool to determine the susceptibility of an individual to develop pre-diabetes and thus diabetes mellitus.

KEYWORDS

Fetuin-A, Pre-diabetes, HOMA-IR.

INTRODUCTION

Pre-diabetes is defined as an intermediate state with plasma glucose levels ranging between normoglycemia and diabetes.In 2017, the International Diabetes Federation estimated that the worldwide prevalence of impaired glucose tolerance (IGT) in adults was 352million and expected to reach 532million by 2045(1).Diagnosing pre-diabetes has been a challenging task and till date it is done based on the levels of plasma glucose and glycated hemoglobin (HbA1c) which are essentially affected by a number of factors which includes diet also. Insulin resistance plays a major role in the development of type 2diabetes(2).Insulin mediates its actions through the insulin receptors (IR) which consist of two extracellular α subunits that bind to insulin and two transmembrane β subunits with intrinsic tyrosine kinase (TK) activity. Binding of in sulin to the IR activates its in trinsic TK activity and results in auto phosphorylation of tyrosine residues of the receptor which is then followed by subsequent phosphorylation of several insulin receptor substrates that mediate the effects of insulin(3).

Fetuin-A, a 60 k Da glycoprotein exclusively produced by liver, binds to insulin receptors in adipose and muscular tissue and inhibits insulin receptor tyrosine kinase activity as well as insulin receptor autophosphorylation in vivo and in vitro(4). Therefore, it may be responsible for promoting insulin resistance and have a role in the pathogenesis of type 2 diabetes mellitus.

Thus, in view of the background of an increasing burden of type 2 diabetes mellitus in our population, we aimed to investigate the role of Fetuin-A in causing insulin resistance in pre-diabetes and type 2 diabetes mellitus in the local population.

METHODS AND MATERIAL

The present study was carried out in the Department of Biochemistry and Department of MedicinePeople's College of Medical Science and CSRD,People's University Bhopal.The study protocol is approved by the DDC, RAC, IEC and UDC Committees.Before enrolment in the study informed written consent had been taken from each subject.The clinical manifestations of disease, personal history of patients were recorded in study proforma.

The study was designed taking 300 human subjects. Out of which 100 age matched healthy subjects were considered as control group, 100 pre-diabetic subjects and 100 type 2 diabetic subjects.

Group I (n=100): Normal healthy control group
Group II (n=100): Pre-diabetic group
Group III(n=100): Type 2 Diabetes Mellitus group

The sample was collected from the outdoor patient department (OPD) and indoor patient department (IPD) of People's Hospital, Bhopal. After confirmed diagnosis by physician patients were enrolled after applying all inclusion and exclusion criteria. These patients were compared with healthy normal subjects on the basis of age, sex, dietary conditions and their life styles.

INCLUSION CRITERIA:

- Patients diagnosed with pre-diabetes and type2 diabetes. ADA (American Diabetes Association) values of FBS, 2 hr glucose and HbA1c were taken into consideration for selection of patient.
- Age between 30-60 years.

EXCLUSION CRITERIA:

- Patients with diagnosis of any other disease other than pre-diabetes & type 2 diabetes mellitus (based on their medical history and physical examination) were excluded.
- Patients on antidiabetic drugs, insulin and corticosteroid were excluded from study.
- Patients below 30 and above 60 years were excluded.

LABORATORY INVESTIGATIONS:

10 ml of blood sample was withdrawn from the anticubital vein following overnight fasting. The blood sample was collected in plain, fluoride and EDTA vacutainers. Samples were centrifuged at 3000 rpm for 10 minutes. Serum was separated and immediately stored in freezer at –20°C till further analysis.The blood sample was analyzed for biochemical parameters like blood sugar (fasting and 2-hr glucose), glycated hemoglobin (HbA1c), Insulin, Fetuin-A. Glucose and HbA1c were analyzed by Cobas c-311 fully automated autoanalyzer (Roche diagnostics). Serum glucose was analyzed by hexokinase method and HbA1c by TINIA (Turbidimetric Inhibition Immunoassay)method. Insulin was estimated by Cobas e-411 fully automated autoanalyzer (Roche Diagnostic) based on sandwich principle. Fetuin-A was assayed using Human AHSG (Fetuin-A) Elisa kit (Sandwich type) from Thermo Fisher Scientific, USA. Physiological parameters were also recorded.

Statistical analysis:
Data analysis were performed using Statistical Package for the Social Sciences, version 16.0 (SPSS, Chicago, Illinois, USA) and Excel (Microsoft Corp., Redmond, WA). The results were expressed as Mean ± Standard Deviation. Independent sample t-test was done for evaluating the results. Pearson correlation coefficient was used to determine the correlation between the Fetuin-A, Glucose (fasting and 2-hr), HbA1c, insulin and HOMA-IR.

RESULTS:
The outcome of the result are as follows

The three groups are equal in numbers for all age and sex groups as we followed age sex matching in the selection of study subjects.

Table 1: The comparison of the variables selected for study among the respondents (controls Vs pre-diabetes) selected for this study

Variables	Class	Frequency	Mean	Standard deviation	Standard error	t value	p value
Waist circumference	Control	100	74.87	7.4	0.74		
	Pre-diabetes	100	80.17	5.75	0.58	-5.654	.001
Waist hip ratio	Control	100	0.80	0.10	0.01		
	Pre-diabetes	100	0.87	0.06	0.01	-6.094	0.001
Body Mass Index	Control	100	22.22	2.79	0.28		
	Pre-diabetes	100	22.57	3.06	0.31	-.841	0.40
FBS	Control	100	83.62	7.69	0.77		
	Pre-diabetes	100	114.58	7.31	0.73	-29.181	0.001
2-hr glucose	Control	100	120.72	10.05	1.01		
	Pre-diabetes	100	163.20	14.77	1.48	-23.783	0.001
HbA1c	Control	100	4.50	0.63	0.06		
	Pre-diabetes	100	6.10	0.25	0.03	-23.658	0.001
Fasting insulin	Control	100	7.20	3.63	0.36		
	Pre-diabetes	100	12.46	3.92	0.39	-9.845	0.001
HOMA_IR	Control	100	1.49	0.80	0.08		
	Pre-diabetes	100	3.47	0.92	0.09	-16.314	0.001
Fetuin-A	Control	100	266.77	31.97	3.20		
	Pre-diabetes	100	281.90	48.22	4.82	-2.616	0.01

Table 1 shows means ± SD of serum levels of Fetuin-A, fasting and 2-hr glucose, HbA1c, insulin and HOMA-IR in controls and pre-diabetics. Significant increase in serum Fetuin-A, fasting and 2-hr glucose, insulin and HOMA-IR was found in pre-diabetic as compared to controls.

Correlation between controls and pre-diabetes

- Fetuin A is weakly correlated with waist circumference ($r = 0.21$; p value <0.01), waist hip ratio ($r = 0.15$; p value <0.05), BMI ($r = 0.23$; p value <0.001), 2-hr glucose ($r = 0.27$; p value <0.001), fasting insulin ($r = 0.20$; p value <0.01).

Table 2: The comparison of the variables selected for study among the respondents (controls Vs diabetes) selected for this study

Variables	Class	Frequency	Mean	Standard deviation	Standard error	t test	p value
Waist circumference	Control	100	74.87	7.40	0.74		
	Diabetes	100	88.14	5.05	0.51	-14.813	0.001
Waist hip ratio	Control	100	0.80	0.09	0.01		
	Diabetes	100	1.01	0.23	0.02	-8.562	0.001
Body Mass Index	Control	100	22.22	2.79	0.28		
	Diabetes	100	29.90	2.56	0.26	-20.306	0.001
FBS	Control	100	83.62	7.69	0.77		
	Diabetes	100	149.78	30.27	3.03	-21.186	0.001
2-hr glucose	Control	100	120.72	10.05	1.01		
	Diabetes	100	255.58	40.07	4.01	-32.642	0.001
HbA1c	Control	100	4.51	0.63	0.06		
	Diabetes	100	8.86	1.39	0.14	-28.487	0.001
Fasting insulin	Control	100	7.19	3.63	0.37		
	Diabetes	100	29.01	5.06	0.51	-35.006	0.001
HOMA-IR	Control	100	1.48	0.80	0.08		
	Diabetes	100	10.68	2.70	0.27	-32.630	0.001
Fetuin-A	Control	100	266.76	31.97	3.20		
	Diabetes	100	336.27	69.71	6.97	-9.062	0.001

Table 2 shows means ± SD of serum levels of Fetuin-A, fasting and 2-hr glucose, HbA1c, insulin and HOMA-IR in controls and diabetics. Significant increase in serum Fetuin-A, fasting and 2-hr glucose, insulin and HOMA-IR was found in diabetic as compared to controls.

Correlation between controls and diabetes

- Fetuin A is moderately positively correlated with waist circumference ($r = 0.5$), BMI ($r = 0.5$), FBS ($r = 0.5$), 2-hr glucose ($r = 0.5$), HbA1c ($r = 0.5$), fasting insulin ($r = 0.5$), and insulin resistance ($r = 0.5$) which are statistically significant ($p < 0.001$).
- Fetuin A is weakly positively correlated with waist hip ratio ($r = 0.34$) which is statistically significant ($p < 0.001$).
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DISCUSSION:
Insulin resistance is one of the most important factor for the development of diabetes mellitus as well as cardiovascular disease(5). Many factors, including fatty acids and cytokines influences the effect of insulin-signalling molecules or through other pathways that interfere with the insulin signaling pathways(6). Fetuin-A is also thought to be involved in the pathogenesis of insulin resistance(7).

We aimed to investigate the possible role of serum Fetuin-A in the development of insulin resistance. We found that serum Fetuin-A levels and insulin resistance values were increased across the spectrum of glycemia and were highest in subjects with diabetes, followed by those with pre-diabetes and lowest in healthy controls which is similar to previous studies(8).A large prospective study with 7 years follow up, has also shown significant association of Fetuin-A with increased risk of future diabetes in those individuals who had elevated glucose levels but not in the diabetic range(9) whereas Mori et al found no significant differences in serum Fetuin-A levels between the type 2 diabetic group and the control group.

Our study showed a significant correlation between elevated serum Fetuin-A and fasting blood sugar, 2-hr glucose, HbA1c and HOMA-IR. These correlations clearly define the role of Fetuin-A in controlling

the action of insulin and maintenance of glucose homeostasis.

CONCLUSION:

Increased Fetuin-A levels had an adverse impact on glycemic outcomes thus sggesting that fasting plasma glucose and Fetuin-A can be used as a tool to determine the susceptibility of an individual to develop pre-diabetes and thus diabetes.

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