Original Research Article

Association of fetuin-A, vitamin D, adiponectin and interleukin-6 with insulin resistance in prediabetes and type 2 diabetes

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Abstract

Background: Diagnosing prediabetes has been a challenging task and till date it is done on the basis of levels of plasma glucose and glycated haemoglobin (HbA1c). Fetuin-A, vitamin D, adiponectin and interleukin-6 (IL-6) can serve as an important marker for dianosing prediabetes. The present study was designed to evaluate the role of these biochemical marker levels in predicting glycaemic outcome in people with pre-diabetes. **Method 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 900 subjects were included, out of which 300 were known type 2 diabetics, 300 were prediabetics and 300 were normal healthy individuals. Laboratory investigations included serum fasting and 2-hour glucose, HbA1c, insulin, fetuin-A, vitamin D, adiponectin and IL-6. Insulin resistance was calculated by Homeostatic model assessment (HOMA-IR). **Results:** We observed that serum Fetuin-A, IL-6, insulin levels and HOMA-IR were significantly higher in known type 2 diabetics as compared to pre-diabetics and control group. Vitamin D and adiponectin levels were lower in type 2 diabetics as compared to pre-diabetics and control group. **Conclusion:** Increased Fetuin-A and IL-6 levels and decreased adiponectin and IL-6 had an adverse impact on glycemic outcomes in pre-diabetes thus suggesting that fetuin A, vitamin D, adiponectin and IL-6 can be used as a tool to determine the susceptibility of an individual to develop pre-diabetes and thus diabetes mellitus.

Keywords: HbA1c (Glycated Hemoglobin), IL-6 (Interleukin-6), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance, DBP (Vitamin D Binding Protein).

Introduction

Diabetes Mellitus is a metabolic condition, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. This leads to an increased concentration of glucose in the blood (hyperglycaemia). Prediabetes is the progeny of diabetes. It is a condition in which individuals have blood glucose levels higher than normal but not as high as diabetes. It is also termed as Impaired Glucose Regulation (IGR) which consist of Impaired Fasting Glucose and/or Impaired Glucose Tolerance (IFG and/or IGT)[1]. It is a reversible condition that increases the risk for diabetes which is associated with insulin resistance or decline in insulin sensitivity. The risk factors are same as for diabetes namely overweight, advanced age, poor diet and excess calories or poor nutrition, lack of physical activity, smoking and family history[2]. Long term diabetes has been associated with microvascular complications such as nephropathy, retinopathy, neuropathy and macrovascular complications as cardiomyopathy, vasculopathy, dermatopathy and atherosclerosis.

Diabetes is a problem necessitating critical intervention especially in India. The prevalence has increased ten-fold from 1970 to 2000 which is 12% from 1.2%.

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It is estimated that 61.3 million people aged 20-79 years live with diabetes in India (2011 estimates). This number is expected to increase to 101.2 million by 2030. There were about 77.2 million people in India with prediabetes as of 2013. The most distressing fact is that the onset age for diabetes has shifted down to a younger age[3]. Prediabetes is commonly an asymptomatic condition, there is always presence of prediabetes before the onset of diabetes. The elevation of blood sugar is a continuum and hence prediabetes cannot be considered an entirely benign condition. The aim of this study is to describe the challenges associated with diagnosis of prediabetes. There are some biochemical markers as fetuin-A, vitamin D, adiponectin and interleukin-6 which are associated with a greater risk of diabetes development and it's complications. Fetuin-A inhibits insulin receptor tyrosine kinase activity through blocking the autophosphorylation of tyrosine kinase and insulin receptor substrate-1(IRS-1), which induces a lower-grade inflammation resulting in insulin resistance[4]. Vitamin D deficiency predisposes individuals to type 2 diabetes, and receptors for its activated form—1α,25-dihydroxyvitamin D3 are present in both ß-cells and immune cells.1,25(OH)2D3 is essential for insulin exocytosis by increasing the expression of calbindin-D28K (Vitamin D Binding Protein-DBP) in β-cells. DBP regulates intracellular calcium levels in ß-cells, and facilitates insulin exocytosis. DBP also plays a protective role by decreasing inflammatory cytokine induced ß-cell apoptosis.T2DM develops due to increase in circulating cytokine as IL-6. Vitamin D acts as a potent immunosupressor and down regulate the transcription of proinflammatory cytokines leading to insulin resistance in muscle

and adipose tissue[5].Adipocytokines is a general term for a bioactive product produced by adipose tissue. It includes inflammatory mediators IL-6 (Interleukin-6) and metabolic regulators (adiponectin). These adipocytokines have been implicated in the development of insulin resistance. Adiponectin has anti-inflammatory, antidiabetic, and anti-atherogenic properties. Research indicates that it improves insulin sensitivity and inflammation. It improves insulin sensitivity by stimulating glucose utilization and fatty acid oxidation in the skeletal muscle and liver through improving AMPactivated protein kinase[6]. When the circulating level of IL-6 is high it causes impaired insulin signaling in hepatocytes and is associated with diabetes[7]. Our literature review has found the importance of abovesaid bio-chemical parameters in the serum of prediabetes and diabetes. This drew our interest in designing a screening programme for early detection of diabetes. Many research papers have not been published in this context in the defined geographic location. Hence, we planned this study.

Aim and Objectives

This study was designed to evaluate the association of fetuin-A, vitamin D, adiponectin and IL-6 with insulin resistance among prediabetic and type 2 diabetic subjects. To achieve the aim we took the following objectives:

1. To assess the level of blood/ serum biochemical parameters such as fasting blood glucose, 2-hr Glucose, HbA1c (glycated haemoglobin), in both prediabetic and type 2 diabetic subjects
2. To know the status of fetuin-A, Vitamin D Adipocytokines (Adiponectin and Interleukin-6), in both prediabetic and type 2 diabetic and compare it with normal healthy group subjects.
3. To see the level of fetuin-A, vitamin-D, adiponectin and IL-6 on the development of insulin resistance by calculating HOMA-IR (Homeostatic Model Assesment of Insulin Resistance).
4. To rule out the association, if any among all the parameters.

Material and Methods

This cross sectional study was carried out in the Department of Biochemistry, People's College of Medical Sciences & Research Centre and Centre for Scientific & Development (CSRD), People's University, Bhopal during July 2017 to July 2019. The blood sample was collected from the outpatient department (OPD) and inpatient department (IPD) of People's Hospital. The study was designed taking 300 human subjects in each arm, in which, 300 age matched healthy subjects (Group I) were considered as control group, 300 as prediabetic subjects (Group II) and 300 as type 2 diabetic subjects (Group III). Ethical principles such as respect for the persons, beneficence and justice were adhered. Ethical clearance was obtained from the research committee and the Institutional Review Board of People's University. Written informed consent was taken from all the subjects. The evaluation involved a full medical history and anthropometric measurements (weight, height, BMI, waist and hip circumferences, waist hip ratio) and arterial blood pressure.

This is a hospital based analytical cross-sectional study and the sample size calculation was done with the help of the experts in that field.

Collection of blood samples

Under strict aseptic conditions, 10 ml of blood sample was withdrawn from the antecubital vein following an overnight fasting of 9 hours.The blood sample for insulin, fetuin-A, vitamin D, adiponectin and interleukin-6 were collected in plain vacutainers. The sample for glucose estimation was collected in fluoride vacutainers. The sample for HbA1c was collected in EDTA vacutainers.

Table 1: Biochemical Parameters and Methods

Sr No.	Study Parameters	Methodology
1.	Glucose	Enzymatic Method (Hexokinase)
2.	HbA1c	Turbidimetric inhibition immunoassay
3.	Insulin & Vitamin D	Electrochemiluminescence Method (ECL)
4.	Fetuin-A, Adiponectin & IL-6	ELISA Method

All the biochemical parameters were estimated by Standard Kit method by using Cobas c311 fully automated analyzer (Roche diagnostics). Hormonal parameters were done on Cobas c411 fully automated immunoassay analyzer (Roche diagnostics) by using cobas kits. Fetuin-A, adiponectin and interleukin-6 were estimated by using Elisa Plate Reader Thermo Scientific Multiskan from Thermo Fisher Scientific. Serum Insulin resistance was estimated by the Homeostasis model assessment (HOMA-IR) and calculated as Fasting Insulin (microU/L) x Fasting glucose (mg/dl)/405.

Calculation and Statistical analysis

The data was entered into Microsoft Excel software package. The entered data were transferred to SPSS 24.0 software (SPSS Inc., Chicago, Illinois, USA) package for analysis. ANOVA test was applied to proportions to test the level of significance. Pearson's correlation was used to study the strength of association. The level of significance was fixed at 0.05 and Confidence interval (CI) was set at 95%.

Results

In our study we have compared anthropometric and biochemical parameters in pre-diabetic, type 2 diabetic and healthy control groups. Anthropometric parameters (BMI, waist circumference, waist to hip ratio) as well as systolic and diastolic blood pressure are statistically significantly differed in pre-diabetic and diabetic group compared to control group.The observations and inference obtained from this study were summarized in the following tables:

Table 2: The socio demographic features of all three respondents (control, prediabetes and type 2 diabetes) selected for this study are as

Age group	Frequency	Percent (%)	Cumulative percent (%)
31 – 40 years	114	38	38
41 – 50 years	93	31	69
51 – 60 years	93	31	100
Total	300	100	100

Table 3: The sex distribution of all the respondents selected for this study

Class	Frequency	Percent	Cumulative percent
Normal	Male	150	50
	Female	150	100
Pre diabetes	Male	150	50
	Female	150	100
Diabetes	Male	150	50
	Female	150	100

Table 4: Comparison of study parameters between the control, prediabetic and type 2 diabetic groups selected for the study

Parameters	Healthy controls	Prediabetes	Type 2 Diabetes	ANOVA
WC(cm)	74.87 ± 7.4	79.95 ± 5.7	84.2 ± 5.4	0.001*
WHR	0.82 ± 0.09	0.87 ± 0.06	0.98 ± 0.23	0.001*
BMI(kg/m2)	22.22 ± 2.79	24.89 ± 2.4	29.25 ± 3.06	0.001*
SBP(mm/Hg)	120 ± 8.03	131 ± 6.4	145.5 ± 15.45	0.001*
DBP(mm/Hg)	76.28 ± 6.9	83.04 ± 7.5	96.33 ± 9.4	0.001*
FBG((mg/dl)	83.62 ± 7.7	114.58 ± 7.3	149.78 ± 30.27	0.001*
2-hr Glucose(mg/dl)	120.72± 10.05	163.2 ± 14.77	255.58 ± 40.07	0.001*
HbA1c(%)	4.5 ± 0.63	6.10 ± 0.25	8.85 ± 1.39	0.001*
Fasting insulin(µIU)	6.09 ± 2.13	7.19 ± 3.63	29.006 ± 5.06	0.001*
HOMA-IR	1.48 ± 0.80	2.04 ± 0.98	10.67 ± 2.7	0.001*
Fetuin-A(pg/ml)	266.77± 31.97	281.9 ± 48.22	336.27 ± 69.71	0.001*
Adiponectin(ng/ml)	6.9 ± 0.30	5.47 ± 0.31	3.98 ± 0.25	0.001*
Interleukin-6(pg/ml)	1.74 ± 0.15	2.03 ± 0.13	3.06 ± 0.35	0.001*
Vitamin D(ng/ml)	28.06 ± 6.63	18.7 ± 4.12	15.10 ± 2.93	0.001*

*** p value significant < 0.001**

This table shows comparison of study parameters between the control, prediabetic and type 2 diabetic groups selected for the study. We see a progressive rise in the mean glucose, HbA1c, fasting Insulin and HOMA-IR among control, prediabetes and type 2 diabetes. The increase is statistically significant.

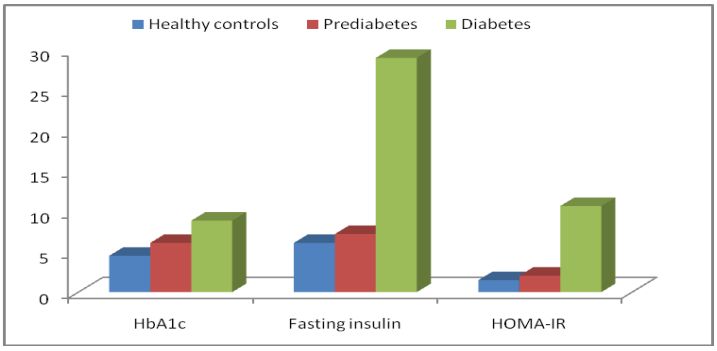

Fig 1: Bar chart showing HbA1c, Fasting insulin & HOMA-IR among 3 group

The mean of Vitamin D and adiponectin biomarker value is least for diabetes as compared to prediabetes and healthy controls which is statistically significant. On the other hand mean value for fetuin-A and IL-6 is the maximum for diabetes when compared to prediabetes.

Correlations among variables in control and pre-diabetic group

1. HOMA-IR is weakly positively correlated with fetuin-A (r = 0.2; p value < 0.01) which is statistically significant.

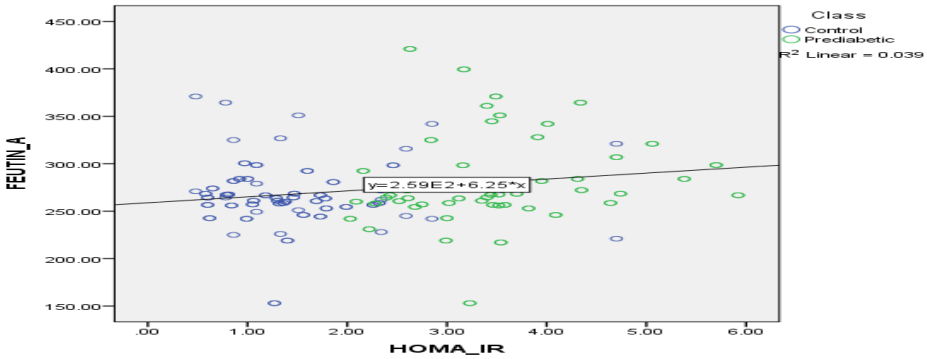

Fig 2: Correlation between HOMA-IR and Fetuin-A in Prediabetes

2. HOMA-IR is moderately negatively correlated with vitamin D (r = - 0.47; p value < 0.01) which are statistically significant.

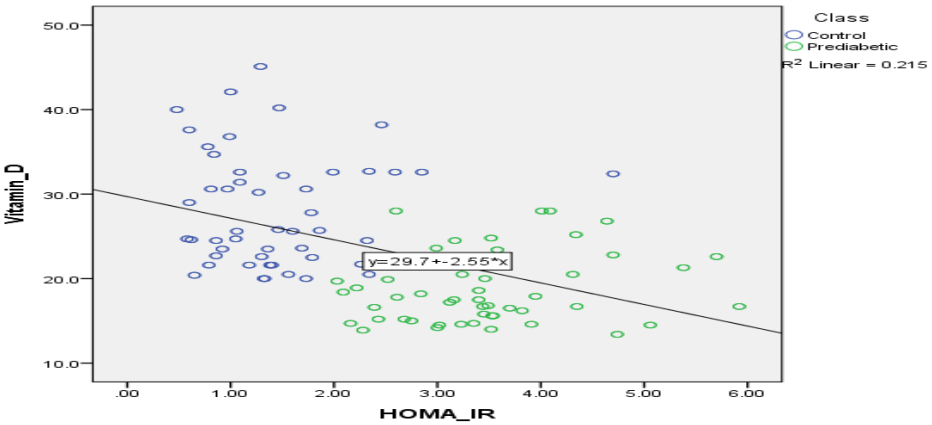

Fig 3: Correlation between HOMA-IR and Vitamin-D in Prediabetes

3. HOMA-IR is strongly negatively correlated with adiponectin (r = - 0.7; p value < 0.01

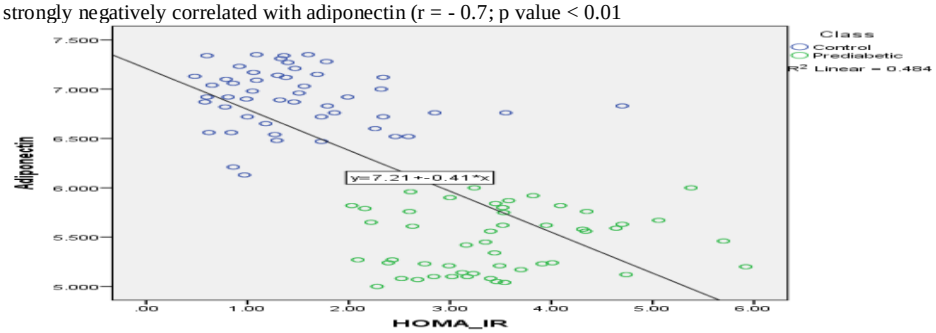

Fig 4: Correlation between HOMA-IR and Adiponectin in Prediabetes

4. HOMA-IR is moderately positively correlated with IL-6 (r = 0.54; p value < 0.01) which is statistically significant.

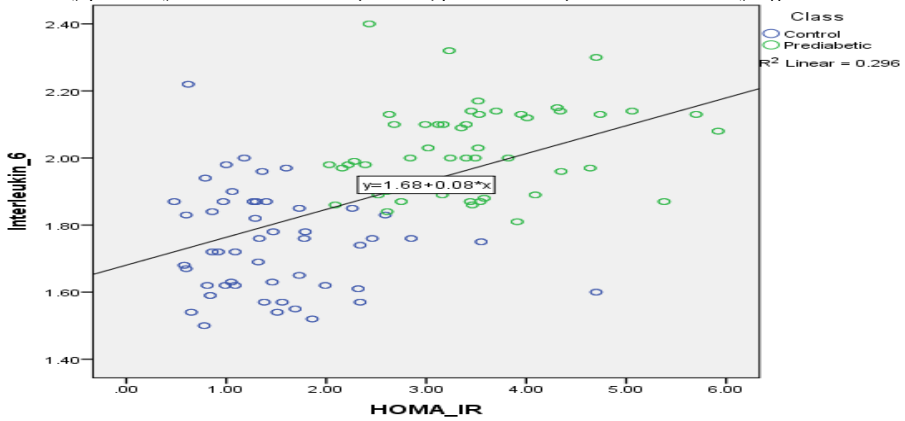

Fig 5: Correlation between HOMA-IR Interleukin-6 in prediabetes

Discussion

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 pre-diabetes and lowest in healthy controls which are 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.From our results, it is evident that vitamin D deficiency in patients with impaired glucose tolerance (pre-diabetes) and type 2 DM is high. Therefore, vitamin D deficiency may affect insulin secretion and insulin resistance- the two methods of pathogenesis of type-2 DM. Several cross-sectional and prospective studies in various populations shows inverse association between circulating 25(OH)D and fasting plasma glucose (FPG) level, impaired glucose tolerance (IGT), HbA1c and incidence of prediabetes. A study conducted by Dutta et al. have investigated the relationship between the vitamin D status and insulin resistance among adult individuals with pre-diabetes, by evaluating the circulating levels of [25(OH)D]. As per the study report from Dutta et.al, the association between vitamin D deficiency among pre-diabetic patients was independent of their BMI status and HbA1c levels[10]. But from our study, we can conclude that there is an association between impaired FPG levels and vitamin D deficiency among pre-diabetic patients[9]. In a study conducted by Holick et al., the authors observed that patients with vitamin D deficiency have the highest insulin resistance[11]. The prevalence of vitamin D deficiency

in our study is similar to that reported by Scragg et al., where the circulating 25(OH)D levels was found to be significantly lower in individuals with newly diagnosed impaired glucose tolerance or prediabetes as compared to normal individuals[12]. In their study, vitamin D levels were not significantly different in individuals with pre-diabetes as compared to those with diabetes or normoglycemia. But in our study we find a significant difference between prediabetes and diabetes group. Gupta et al, suggested that 25[OH]D levels were lower in prediabetic patients and affected by age, sex and BMI[13]. In our study also we found a negative correlations between serum 25[OH]D level and BMI and fasting blood glucose. Moreover, low serum 25[OH]D level was strictly correlated with elevated insulin level. The risk of insulin resistance was increased in patients with vitamin D deficiency. Forouhar et al demonstrated that there is negative correlation between insulin resistance and 25[OH]D level[14]. In prediabetic patients, pancreatic early phase insulin release is impaired, together with increased serum insulin levels[15,16]. This situation accelerates the development of insulin resistance and overt diabetes in prediabetic patient[17]. In the condition of obesity the number and size of adipocytes increases with further increase of the total fat mass[18]. Visceral fat compartments are largely responsible for the secretion of adiponectin, when compared to subcutaneous deposits. It shows the close association between visceral obesity and metabolic disease; however, in vitro and in vivo studies performed in humans have shown that adipocytes with exhausted lipid storage, filled with fatty acids, and located in the intra-abdominal region can inhibit transcription of the adiponectin gene by secreting inflammatory and angiogenic factors, reducing its plasma levels[19].This condition may also play an important role in the development of a chronic low-grade pro-inflammatory state associated with adipose tissue dysfunction and diabetes. Enlarged adipocytes leads to an imbalance between pro- and anti-inflammatory adipokines[20, 21]. The secretions of pro-inflammatory cytokines IL-6, IL-8 have been positively correlated with adipocyte size[22]. Significant correlation with insulin resistance makes adiponectin a powerful prognostic marker for diabetic risk in patients who do not yet manifest T2DM. Interleukin-6 (IL-6), another biomarker of importance in our study, is a proinflammatory cytokine that causes the development of insulin resistance. This is done by the generation of inflammation by controlling differentiation, migration, proliferation and cell apoptosis. In vitro studies have shown that IL-6 treatment downregulates adiponectin mRNA suggesting a negative role of IL-6 in adiponectin regulation[23] Experimental studies and cross-sectional analyses has shown that circulating IL-6 is associated with hyperglycemia and insulin resistance. It has also been shown that circulating IL-6 increases with the degree of insulin resistance[24, 25]. In our study also we have got a positive coorelation of IL-6 with HOMA-IR and negative correlation of adiponectin with HOMA-IR in both pre-diabetic and type 2 diabetic conditions.

Conclusion

From our data it can be summarized that there is a significant change in fetuin-A, vitamin D, adiponectin and IL-6 levels in prediabetic, and diabetic population as compared to healthy controls of population of Bhopal region. Fetuin-A and IL-6 shows a positive correlation whereas vitamin D and adiponectin shows a negative correlation with insulin resistance.

Clinical Significance

Screening for these biomarkers at an early stage might prove fruitful in the early detection of the development of insulin resistance and type 2 diabetes mellitus and positively delay the onset of this non communicable disease. Further, this will provide an opportunity for the research and invention of drugs to block this inflammatory pathway and in turn the development of type 2 diabetes. There might be potential beneficial role of vitamin D supplementation and improving glycemic status in type 2 diabetics.

Strength and Limitations

Our study is done on a representative large sample. We matched the age and sex to prevent their confounding. Pearson's correlation was done to assess the strength of association.The use of a cross sectional study limits the interpretation of the causal pathway. Hence, further longitudinal studies in a larger sample can be taken up to ascertain the cause-effect relationship. The same needs evaluation in a larger cohort to establish validity and confirm the correlation factors.

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