

Inflammatory Markers in Pre-diabetes and Diabetes: A Comparative Study

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ABSTRACT

Background: Diabetes is a metabolic disorder associated with chronic inflammation. It is preceded by pre-diabetic phase that is also influenced by the inflammatory mechanisms which finally culminate into diabetes and its associated complications. Thus the main objective of this study was to assess the level of inflammatory mediators in pre-diabetic and diabetic patients. **Methods:** This case control study was conducted with 100 controls, 145 pre-diabetic patients and 126 diabetic patients in Santosh medical College and Hospital, Ghaziabad. Serum routine parameters like fasting glucose, HbA1c, lipid and inflammatory mediators like adiponectin, fibrinogen, IL-6, CRP and uric acid were estimated using kit based methods. **Results:** We observed significantly low adiponectin and significantly high CRP, IL-6, fibrinogen and uric acid in pre-diabetic and diabetic patients compared to controls. The level showed gradual decrease from control-pre-diabetic-diabetic groups in case of adiponectin while the trend was increasing in case of CRP, IL-6, fibrinogen and uric acid. We also found significant negative correlation of adiponectin with CRP, IL-6, fibrinogen and uric acid in both the patient groups but the correlation with uric acid in pre-diabetic patients was insignificant. **Conclusion:** These results reveal the involvement of inflammatory mechanisms in progression from normoglycemia to impaired fasting glucose and finally to hyperglycemia. Therefore the development of mechanisms that aid in reducing pro-inflammatory and alleviating anti-inflammatory mediators may be fruitful in reducing diabetes risks.

Keywords: Cardiovascular disease, Diabetes, Inflammation, Pre-diabetes.

INTRODUCTION

Chronic inflammation is one of the crucial factors to drive the pathogenesis of diabetes. Diabetes is a metabolic disorder with altered cytokine profiles that can be observed as decreased level of anti-inflammatory cytokines like adiponectin, and increased level of pro-inflammatory cytokines such as CRP, IL-6, TNF- α etc. The impairment in these cytokine profiles induces insulin resistance in liver, muscles and adipose tissues thereby leading to blood glucose dysregulation.^[1,2] Several cross sectional studies have established the link of obesity and insulin resistance with inflammatory markers and endothelial dysfunctions. Obesity, that drives metabolic and adipocyte stress has emerged as an important contributor to diabetes and associated cardiovascular risks. Insulin resistance associated with obesity along with innate immune system activation and production of adipokines is the

connecting bridge between inflammation and diabetes.^[3,4]

Though diabetes and inflammation are shown to be associated directly, there is still lack of well defined cause and effect relationship. However, it is postulated that the alteration in level of pro-inflammatory mediators is compensated by changes in the level of anti-inflammatory mediators. As the person progresses to hyperglycemic state from normoglycemic state, such balance is hindered leading to systemic disorders.^[5] It is also evident that individuals before progressing to diabetes undergo a latent phase known as pre-diabetic state which may be defined as the state in which the fasting or post prandial blood glucose levels are above the normal range but below than the range required for diagnosis of diabetes.^[6] Further various studies have also established the link between hyperglycemia induced systemic inflammation and cardiovascular disease (CVD), hence it may be instigated that even pre-diabetic patients are at a high risk of developing cardiovascular disease in future. One of the potent risks of CVD is atherosclerosis which is the consequences of inflammatory mechanisms. Further dyslipidemia, one of characteristic features of diabetes also supports the development of cardiovascular disease.^[7] Some markers of

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inflammation like adiponectin, CRP, IL-6, fibrinogen and uric acid are well known and effective predictors of future CVD risk in diabetes. However, previous studies have created a state of dilemma as some reported these markers to predict the definite risk while some failed to confirm such reports. Also limited data are available correlating the inflammatory parameters in pre-diabetic and diabetic patients in Indian population. Thus, in this study we aimed to establish whether dysregulation of inflammatory mediators are evident in pre-diabetic patients and whether their measurement could predict overt diabetes. We have focussed on various inflammatory markers and investigated their association with disease progression from normoglycemia to diabetic state (hyperglycemia) via pre-diabetic state (impaired fasting glucose) on Indian population.

MATERIALS AND METHODS

This was a cross sectional study conducted in Santosh Medical College and Hospital involving 100 healthy controls, 145 pre-diabetic patients and 126 diabetic patients. Patients without any history of inflammatory disorder, pregnancy, and cardiovascular diseases etc that alter the level of inflammatory markers were enrolled. The study was approved by the ethical board of institution.

There was voluntary participation of each participant in this research and written consents were also obtained from each of them. Age, BMI (body mass index), WHR (waist hip ratio) of each patient were recorded. Biochemical parameters like fasting sugar, glycosylated haemoglobin (HbA1c), cholesterol (CHO), HDL cholesterol, triglyceride (TG) and inflammatory parameters like adiponectin, CRP (C reactive protein), IL-6 (Interleukin 6), fibrinogen and uric acid were measured in each patient.

Fasting sugar was estimated by GODPOD method, HbA1c was measured using ion exchange resin method while total cholesterol, HDL and TG were analysed by CHOD-POD, CHOD-POD/phosphotungstate method and GPO-PAP method respectively. LDL was derived using Friedwald's equation,^[8] i.e. $LDL = \text{Total Cholesterol} - (\text{HDL} + \text{VLDL})$ and $VLDL = TG/5$. Inflammatory markers like adiponectin and IL-6 were investigated by ELISA while CRP and fibrinogen were quantified respectively by immunoturbidimetric method. Uric acid was assayed by uricase method.

Statistical analysis

All the study parameters (age, BMI, WHR, fasting sugar, HbA1c, cholesterol, HDL, TG, LDL, adiponectin, CRP, IL-6, fibrinogen and uric acid) were expressed as mean \pm sd. The difference in these parameters between control and pre-diabetic, control and diabetic, and pre-diabetic and diabetic groups was investigated using student's unpaired t test.

Similarly the association between inflammatory markers and other study parameters mentioned above was determined using Pearson's correlation coefficient. The p value less than 0.05 was reported statistically significant.

RESULTS

The comparison of basic parameters among three groups (control, pre-diabetic and diabetic patients) is shown in [Table 1]. There was significant difference in age BMI, WHR, fasting glucose, HbA1c, cholesterol, triglyceride (TG) and LDL between control and pre-diabetic groups. Significant differences in the levels of basic parameters were also observed between control and diabetic groups. When the comparison was made among pre-diabetic and diabetic patients, statistical significance was observed in case of fasting glucose, HbA1c, CHO, HDL and TG ($p < 0.05$).

[Table 2] represents the level of inflammatory markers among control, pre-diabetic and diabetic patients. We observed significantly lower level of adiponectin and significantly higher levels of CRP, IL-6, fibrinogen and uric acid in pre-diabetic and diabetic patients when compared with control group. However, significant difference could not be observed in case of uric acid on comparison between pre-diabetic and diabetic patients ($p > 0.05$).

We also correlated inflammatory markers with basic parameters in pre-diabetic [Table 3] and diabetic patients [Table 4]. In case of pre-diabetic patients, adiponectin was significantly and negatively correlated with WHR, fasting sugar, HbA1c, cholesterol, TG and LDL, and positively with HDL. CRP showed significant positive correlation with HbA1c, cholesterol and LDL and, significant negative correlation with HDL. Similarly IL-6 was correlated positively with HbA1c and TG, and negatively with HDL. The correlations were statistically significant. Fibrinogen correlated significantly and positively with glucose, HbA1c, cholesterol and LDL and, with HDL it was significantly negative. In case of uric acid, we could observe significant positive correlation only with BMI, WHR and fasting glucose.

In case of diabetic patients age BMI, WHR, fasting sugar, HbA1c, cholesterol, TG and HDL were correlated negatively and significantly while HDL showed significant positive correlation with adiponectin. Similarly CRP correlated inversely with HDL and linearly with BMI, WHR, fasting sugar, HbA1c, cholesterol, TG and LDL. The correlation was statistically significant. IL-6 was correlated significantly with all the basic parameters but the correlation with HDL was negative. Similar was the case with fibrinogen but the correlation was significant only with fasting sugar, HbA1c, cholesterol, HDL and LDL. In case of uric acid, except for age and HDL, it was correlated

significantly with rest parameters and the correlation was positive.

We also assessed correlation of adiponectin with CRP, IL-6, fibrinogen and uric acid in both pre-

diabetes and diabetes. Adiponectin showed significant inverse association with CRP, IL-6, fibrinogen and uric acid in both the patients while for uric acid such association was observed in diabetic patients only [Table 5].

Table 1: Comparison basic parameters in Control, Pre-diabetic and Diabetic groups

Parameter	Control (C)	Pre-diabetes (PD)	Diabetes (D)	P(C/PD)	P(C/D)	P(PD/D)
Age (years)	42.87±7.87	48.04±6.78	49.67±10.26	<0.001**	<0.001**	0.09
BMI	23.42±2.1	23.99±2.4	24.35±2.72	0.03*	<0.003**	0.27
WHR	0.85±0.08	0.91±0.12	0.9±0.12	<0.001**	<0.001**	0.67
Glucose (mg/dL)	84.53±7.24	116.63±5.15	160.49±40.15	<0.001**	<0.001**	<0.001**
HbA1c (gm%)	5.05±0.53	5.87±0.44	6.36±0.89	<0.001**	<0.001**	<0.001**
CHO (mg/dL)	173.27±13.58	186.64±25.98	195.59±35.68	<0.001**	<0.001**	0.01**
HDL (mg/dL)	49±5.18	48.19±4.49	46.12±4.73	0.19	<0.001**	0.004**
TG (mg/dL)	105±21.27	110.37±20.96	123.1±37.44	0.04*	<0.001**	<0.001**
LDL (mg/dL)	103.1±13.2	116.28±28.21	124.8±35.14	<0.001**	<0.001**	0.008**

Statistically significant: *→p<0.05 **→p<0.01

Table 2: Comparison of markers of inflammation in Control, Pre-diabetic and Diabetic groups

Parameter	Control (C)	Pre-diabetes (PD)	Diabetes (D)	P(C/PD)	P(C/D)	P(PD/D)
Adiponectin (ug/mL)	9.01±2.82	8.15±1.87	6.84±1.98	<0.001**	<0.001**	0.04*
CRP (mg/L)	2.81±1.13	4.17±1.36	5.15±1.73	<0.001**	<0.001**	<0.001**
IL-6 (pg/mL)	4.31±1.8	5.87±1.6	7.51±2.25	<0.001**	<0.001**	<0.001**
Fibrinogen (mg/dL)	331.18±58.61	346.58±55.78	369.6±61.38	0.03*	<0.001**	0.001**
Uric acid (mg/dL)	4.47±0.76	4.64±1.04	6.33±1.89	0.12	<0.001**	<0.001**

Statistically significant: *→p<0.05 **→p<0.01

Table 3: Correlation of inflammatory markers with basic parameters in pre-diabetic groups

Parameters	Adiponectin (r)	CRP (r)	IL-6 (r)	Fibrinogen (r)	Uric acid (r)
Age	-0.14	0.05	0.09	0.01	0.03
BMI	-0.09	0.01	0.05	0.06	0.21*
WHR	-0.22**	0.1	0.1	0.14	0.32**
Glucose	-0.21*	0.16	0.14	0.27**	0.18*
HbA1c	-0.29**	0.2*	0.23**	0.3**	0.13
CHO	-0.25**	0.24**	0.02	0.18*	0.16
HDL	0.31**	-0.19*	-0.22**	-0.31**	-0.06
TG	-0.19*	0.14	0.26**	0.07	0.09
LDL	-0.25**	0.22**	0.01	0.2*	0.14

Statistically significant: *→p<0.05 **→p<0.01

Table 4: Correlation of inflammatory markers with basic parameters in diabetic groups

Parameters	Adiponectin (r)	CRP (r)	IL-6 (r)	Fibrinogen (r)	Uric acid (r)
Age	-0.27**	0.08	0.19*	0.13	0.02
BMI	-0.47**	0.38**	0.33**	0.14	0.21*
WHR	-0.34**	0.38**	0.26**	0.16	0.23**
Glucose	-0.42**	0.52**	0.28**	0.21*	0.46**
HbA1c	-0.5**	0.52**	0.39**	0.22*	0.35**
CHO	-0.42**	0.69**	0.46**	0.27**	0.37**
HDL	0.32**	-0.5**	-0.34**	-0.29**	-0.09
TG	-0.44**	0.53**	0.39**	0.12	0.23**
LDL	-0.37**	0.65**	0.43**	0.29**	0.34**

Statistically significant: *→p<0.05 **→p<0.01

Table 5: Correlation between Adiponectin and other inflammatory markers in pre-diabetic and diabetic groups

Parameters	Pre-diabetes (r)	Diabetes (r)
CRP	-0.32**	-0.6**
IL-6	-0.2*	-0.49**
Fibrinogen	-0.5**	-0.21*
Uric acid	-0.14	-0.2*

Statistically significant: *→p<0.05 **→p<0.01

Our study reveals the presence of chronic inflammation in pre-diabetic and diabetic patients. The ongoing inflammatory mechanisms further reflect the disease severity and the risk of future complications. Hyperglycemia stimulated overproduction of AGEs (Advanced glycation end products) and oxidative stress induce chronic and low grade inflammation in diabetic patients. In the recent years adipose tissue has emerged as a prominent cause of inflammatory phenomenon

DISCUSSION

occurring in both pre-diabetic and diabetic patients and further investigations are sought in this regard. Thus, in this study we evaluated the levels of inflammatory markers such as adiponectin, CRP, IL-6, fibrinogen and uric acid in pre-diabetic and diabetic patients, and compared that with the healthy controls.

Adiponectin is an adipokine from adipose tissue and is anti-diabetic in action. Several clinical studies have documented inverse association between adiponectin and diabetic risk. In a diabetic prevention program study, people at a risk of diabetes were followed up till they progressed to diabetes. A strong correlation was observed between low level of adiponectin and onset of diabetes.^[9] As per Shrestha S *et al*,^[10] and Diwan AG *et al* adiponectin was significantly low in diabetic patients compared to controls, which was similar to our results.^[11] Jiang *et al*,^[12] and Pauer *et al*,^[13] further confirmed our results as they also reported significant difference in the level of adiponectin in pre-diabetic and diabetic patients with regards to controls.

CRP, a well characterised acute phase protein produced by liver and adipose tissue (mediated by IL-6), is an important risk factor of diabetes and its macrovascular complications. We observed significantly high CRP level in both pre-diabetic and diabetic patients compared to control groups. Our result was supported by that of Chandrika N *et al*,^[14] and Petchiappan V *et al*,^[15] who also documented orderly increase of CRP from normoglycemia to impaired fasting glucose to hyperglycemia. Consistent results were also provided by Shrestha S *et al*,^[10] Sabanayagam C *et al*,^[16] Gupta AK *et al*,^[17] and Pradhan AD *et al*.^[18]

IL-6 is pro-inflammatory cytokine of adipocytes, endothelial cells, leucocytes and skeletal muscles. Experimental studies have shown positive association of IL-6 with insulin resistance and hyperglycemia. We found gradual increase in level of IL-6 from control to pre-diabetic to diabetic groups. Upadhyaya S *et al*,^[19] also demonstrated the similar result. The authors also documented low adiponectin/IL-6 ratio in pre-diabetic and diabetic patients. Rasheed MK *et al*,^[20] and Jain SK *et al*,^[21] also reported high IL-6 in diabetic patients.

Fibrinogen is another important acute phase protein with significant role in diabetic vascular disease. Like CRP and IL-6, the level of fibrinogen in our study showed increasing trend from control to hyperglycaemic group which was in accordance with the result of Kafle DR *et al*,^[22] James JS *et al*,^[23] and Gupta P *et al*.^[24] These authors also suggested high fibrinogen in diabetic patients. The levels were further high in those patients with CAD (Coronary artery disease).

Uric acid, an end product of purine metabolism, can also serve as an important inflammatory marker that mediates diabetic complications. We documented

significantly high uric acid level in pre-diabetic and diabetic patients compared to controls but on comparing between the two patient groups, significant difference could not be established. Khan SA *et al*,^[25] demonstrated high uric acid level in pre-diabetic and diabetic patients thereby suggesting important role of uric acid in progression of pre-diabetes and diabetes from normoglycemic phase. However, in contrast to these reports Rabari K *et al*,^[26] and Srikanth S *et al*,^[27] showed decreasing trend of uric acid from pre-diabetic to diabetic to control groups thus indicating requirement of further researches.

In this study we correlated the inflammatory markers with basic parameters in both the patients groups (pre-diabetic and diabetic). Similar to the previous studies CRP, IL-6, fibrinogen and uric acid were correlated positively with age, BMI, WHR, fasting glucose, cholesterol, TG and LDL, and negatively with HDL. In case of adiponectin the correlation was positive with HDL and negative with the other parameters.^[17,28,29] The level of statistical significance was achieved more in case of diabetic patients.

In the present study adiponectin was correlated with other inflammatory markers too (CRP, IL-6, fibrinogen and uric acid). We observed statistically significant negative correlation. However, in case of pre-diabetic patients such significant inverse association with uric acid could not be obtained. Our result was in accordance with Rasheed MK *et al*,^[19] and Kluppenholz B *et al*,^[30] who reported negative association of adiponectin with CRP and IL-6, Urbanavicius V *et al*,^[31] Wei S *et al*,^[32] and Gonzalez SJL *et al*,^[33] who documented inverse relationship between adiponectin and uric acid.

CONCLUSION

From our study it can be summarised that diabetes is an inflammatory disease marked with increased level of inflammatory molecules like CRP, IL-6, fibrinogen and uric acid, and decreased level of anti-inflammatory molecules like adiponectin. Before progressing to overt diabetes, an individual experiences a latent phase known as pre-diabetic phase. From our study it is also evident that the inflammatory mechanisms pre-exist in this latent state too since the anti-inflammatory and inflammatory mediators respectively showed gradual decrease and increase from control to pre-diabetic to diabetic groups. The inflammatory mechanism is also linked to development of diabetic vascular diseases that further increases the mortality risk in these patients. Since pre-diabetic phase is considered last option to prevent diabetes and associated complications there is necessity to develop novel approaches (therapeutic or non therapeutic), so that they may aid in increasing the level of anti-

inflammatory mediators like adiponectin and decreasing that of inflammatory mediators (CRP, IL-6, fibrinogen and uric acid) thereby by reducing the burden of diabetes. However further investigation are also recommended.

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