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GLYCEMIC STATUS AND THE MARKERS OF INFLAMMATION: A COMPARATIVE STUDY IN PATIENTS WITH PRE-DIABETES AND DIABETES

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Abstract

Background: Subclinical inflammation characterized by elevated inflammatory markers is found in diabetic patients. Inflammation, an important cardiovascular risk factor, is elevated in diabetics with poor glycemic control than those with good control.

Aim: To study the effect of glycemic status on inflammatory markers in pre-diabetes and diabetes.

Methods: This study included 300 subjects divided into 3 groups; Control: 100, Pre-diabetes: 100 patients and Diabetes: 100 patients. Basic details of all the participants like age and gender were recorded and laboratory investigations like fasting blood sugar (FBS), glycosylated hemoglobin (HbA1c), IL-6, CRP, fibrinogen, uric acid and adiponectin were conducted.

Results: Compared to controls, the levels FBS, HbA1c, IL-6, CRP, fibrinogen and uric acid were elevated and adiponectin was decreased in pre-diabetes and diabetes. The inflammatory parameters (IL-6, CRP, fibrinogen, uric acid and adiponectin) were significantly correlated with glycemic parameters (FBS, HbA1c) in diabetes, i.e. r=0.28, r=0.55, r=0.2, r=0.48 and r=-0.4 respectively in case of FBS and r=-0.39, r=0.48, r=0.21, r=0.33 and r=-0.53 respectively for HbA1c. Similarly, in pre-diabetes, FBS correlated significantly with adiponectin (r=-0.19), fibrinogen (r=0.29) and uric acid (r=0.18) while that with HbA1c was significant with adiponectin (r=-0.31), IL-6 (r=0.25), CRP (r=0.21) and fibrinogen (r=0.3).

Conclusion: The strong correlations observed between glycemic control parameters and inflammation parameters in pre-diabetes and diabetes suggested the crucial involvement of inflammation in the diabetes development. So better control of glycemia can cause significant reduction in inflammation and arrest the health burden.

Key words: Glycemic control, Pre-diabetes, Diabetes, Inflammation.

INTRODUCTION

Diabetes, a serious and devastating public health problem is increasing exponentially worldwide. Vascular complications such as macrovascular and microvascular complications affect the entire organs of human body [1]. Macrovascular complications that comprised of cardiac diseases and stroke contribute to around 50% mortality in diabetic patients [2]. Complications like retinopathy, nephropathy and neuropathy account for the microvascular complications [3]. These complications have increased prodigious burden to diabetes since the risk of cardiovascular disease is increased by 2-4 folds in diabetic subjects [4]. Therefore there is a dire to prevent and control hyperglycemia via suitable approaches. The common measures to assess glycemic control are fasting blood sugar (FBS), post prandial blood sugar (PPBS) and glycosylated hemoglobin (HbA1c). Of these, HbA1c is extensively used marker for glycemic control. High HbA1c level indicates poor glycemic control that significantly increases the risk of atherovascular diseases [5]. HbA1c implicates the glycemic status of over previous 8-12 weeks and thus serves as a useful indicator of diabetes progression and onset of its complications [6]. Not only in diabetic patients, HbA1c also acts as marker of CVD in healthy individuals too [7].

The interesting finding from previous research is that hyperglycemia induces production of inflammatory molecules in adipocytes and acute phase proteins in

liver [8]. Subclinical systemic inflammation characterised by increased concentrations of inflammatory mediators is the main contributor of diabetes development, since it drives insulin resistance [9].

Hyperglycemia, inflammation and atherosclerosis are interrelated. It has also been shown that inflammatory responses are triggered by hyperglycemia induced protein glycation leading to increased levels of inflammatory mediators [10]. Few previous studies have assessed the relationship between glycemic control and inflammation. However the results of those studies are inconsistent as some could report significant association while some failed to report. Also not many researches are available correlating the inflammation with glycemic status in pre-diabetic patients compared to diabetes. Thus the main objective of our study was to determine effect of glycemic control (in terms of fasting blood sugar/FBS and HbA1c) on the levels of inflammatory mediators (CRP, IL-6, fibrinogen, uric acid and adiponectin) in hyperglycemic patients (pre-diabetic and diabetic patients) and to provide insight if proper glycemic control can reduce inflammation and CVD risks.

Materials and methods

Inclusion Criteria

The patients interested to participate voluntarily in the research were included.

1. Patients with Pre-diabetes (Impaired Fasting Glucose)

2. Patients with Type 2 Diabetes

Exclusion Criteria

Patients with asthma, chronic obstructive pulmonary disease (COPD), malignancies, cardiac disease, renal diseases, hepatic diseases, gout and arthritis, type 1 diabetes mellitus and any other causes that altered the level of inflammatory markers were excluded.

With total of 300 participants, this study was initiated in Santosh Medical College and Hospital, Ghaziabad. The participants were categorised as control (100), Pre-diabetes (100) and Diabetes (100). After ethical approval from the institution, blood samples were collected; serum was separated and stored at -80^{0}C until analysis. Biochemical parameters like FBS, HbA1c and inflammatory markers (CRP, IL-6, fibrinogen, uric acid and adiponectin) were estimated in serum samples. Whole blood was used for estimation of HbA1c. All the parameters were assessed using standard kit based methods as follows:

- FBS: Glucose oxidase peroxidase method
- HbA1c: Ion exchange resin method
- Uric acid: Caraway's method
- CRP and Fibrinogen: Immunoturbidimetric method
- IL-6 and Adiponectin: Enzyme linked immunoadsorbent assay.

Statistical analysis

The comparative analysis of the included parameters was done by student's t test (unpaired) and ANOVA. The values were represented in the form of mean±sd. The correlation between glycemic and inflammatory parameters was evaluated with Pearson's correlation coefficient (r). P value less than 0.05 denoted statistical significance.

Result

Figure 1 and Figure 2 respectively represent distribution of participants based on age and gender.

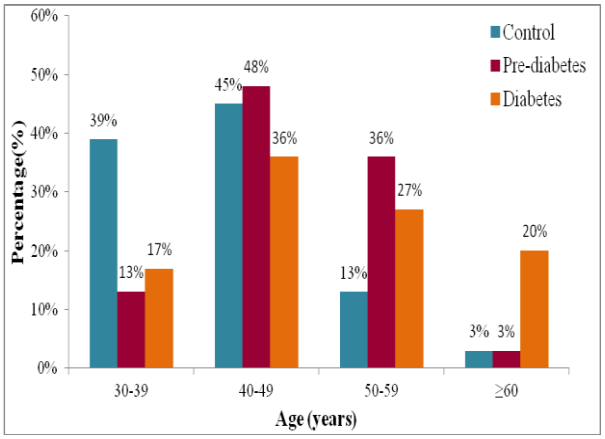

Figure 1: Agewise distribution of participants

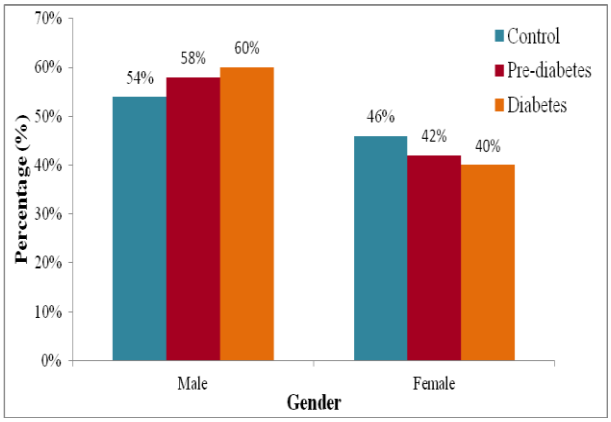

Figure 2: Genderwise distribution of participants

Table 1: Comparison of study parameters among Control, Pre-diabetes and Diabetes

Parameter	Control (C)	Pre-diabetes (P)	Diabetes (D)	p(C/P)	p(C/D)	p(P/D)
Age (years)	40.37±5.27	46.04±6.18	47.07±9.66	<0.001**	<0.001**	0.07
BMI	22.48±2.41	24.19±2.4	24.35±2.77	0.04*	<0.002**	0.29
Glucose (mg/dL)	81.33±7.14	115.43±5.75	168.11±38.05	<0.001**	<0.001**	<0.001**
HbA1c (gm%)	5.17±0.53	5.88±0.29	6.12±0.89	<0.001**	<0.001**	<0.001**
Adiponectin (µg/mL)	9.36±2.51	8.05±1.77	6.89±1.58	<0.001**	<0.001**	0.02*
CRP (mg/L)	2.86±1.03	4.82±1.63	5.35±1.44	<0.001**	<0.001**	<0.001**
IL-6 (pg/mL)	4.36±1.77	5.88±1.63	7.81±2.07	<0.001**	<0.001**	<0.001**
Fibrinogen (mg/dL)	338.15±49.64	350.58±52.81	372.6±60.88	0.02*	<0.001**	0.001**
Uric acid (mg/dL)	4.05±0.71	4.11±1.01	6.53±1.59	0.18	<0.001**	<0.001**

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

In table 1, the comparison of the concentrations of assessed parameters between the three participant groups is shown. The concentrations of FBS, HbA1c, uric acid, CRP, IL-6 and fibrinogen showed gradual increase from control group to diabetic group while that of adiponectin followed decreasing pattern. On comparing between control vs diabetic group and pre-diabetic vs diabetic group, significantly high values were achieved for all the parameters in both the patient categories while in case of control vs pre-diabetic group comparison, such significant difference could not be achieved for uric acid.

Table 2: Association of FBS with inflammatory markers in Pre-diabetes

FBS	No.	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
100-110	13	8.48±2.28	3.95±1.26	5.52±1.45	322.97±66.75	4.23±1.08
110-120	54	8.23±1.69	4.14±1.3	5.88±1.58	349.63±48.8	4.63±0.93
120-130	33	7.89±1.97	4.29±1.5	5.98±1.67	351±60.78	4.81±1.17
ANOVA (p)		0.48	0.636	0.564	0.139	0.117
r		-0.19*	0.14	0.11	0.29**	0.18*

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

Table 3: Association of HbA1c with inflammatory markers in Pre-diabetes

HbA1c	No.	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
4.5-5.5	17	8.89±1.8	3.71±1.12	5.13±1.53	332.72±52.44	4.37±0.76
5.5-6.5	74	8.04±1.84	4.23±1.41	5.95±1.53	349.24±55.67	4.7±1.05
6.5-7.5	9	7.3±1.84	4.63±1.08	6.57±1.83	354.65±64.33	4.71±1.41
ANOVA (p)		0.032*	0.102	0.014*	0.344	0.318
r		-0.31**	0.21*	0.25**	0.3**	0.1

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

Tables 2 and 3 demonstrate the association of FBS and HbA1c with the levels of inflammatory mediators in pre-diabetic participants. Adiponectin showed significant negative correlation with FBS (r=-0.19) and HbA1c (r=-0.31). Fibrinogen (r=0.29) and uric acid (r=0.18) showed significant linear association with FBS while with HbA1c such linear association was given by CRP (r=0.2), IL-6 (r=0.25) and fibrinogen (r=0.3) only.

Table 4: Association of FBS with inflammatory markers in Diabetes

FBS	No.	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
125-200	84	7.12±1.92	4.84±1.59	7.2±2.21	364.94±60.81	6.07±1.73
200-275	6	5.59±1.12	6.16±0.83	9.23±1.27	391.74±44.18	6.28±2.26
275-350	5	4.94±1.51	7.31±2.18	9.37±2.13	398.85±90.67	7.85±1.24
350-425	5	5.06±1.9	7.35±0.83	8.93±1.97	397.63±45.76	9.51±1.21
ANOVA (p)		0.001**	<0.001**	0.004**	0.248	<0.001**
r		-0.4**	0.55**	0.28**	0.2*	0.48**

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

Table 5: Association of HbA1c with inflammatory markers in Diabetes

HbA1c	No.	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
4.5-5.5	11	8.39±1.87	4.11±1.54	6.61±1.74	343.51±53.02	5.82±1.78
5.5-6.5	53	7.26±1.84	4.68±1.38	6.88±2.08	364.4±64.25	5.92±1.65
6.5-7.5	24	6.07±1.62	5.8±1.91	8.76±2.37	383.59±51.79	7.01±1.83
7.5-8.5	8	5.52±1.36	6.43±1.04	8.43±1.73	384.58±63.47	6.48±2.45
8.5-9.5	4	4.05±1.33	7.91±0.95	8.96±1.76	398.56±77.79	8.86±1.73
ANOVA (p)		<0.001**	<0.001**	<0.001**	0.179	0.001**
r		-0.53**	0.48**	0.39**	0.21*	0.33**

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

Tables 4 and 5 represent the association of FBS and HbA1c with the levels of inflammatory mediators in diabetic participants. Significant decrease in adiponectin and significant increase in CRP, IL-6 and uric acid levels with the increase in FBS were observed. Similar results were obtained in case of HbA1c. Adiponectin showed significant negative correlation with FBS (r=-0.4) and HbA1c (r=-0.53). Similarly the correlations of IL-6 (r=0.28, r=0.39), CRP (r=0.55, r=0.48), fibrinogen (r=0.2, r=0.21) and uric acid (r=0.48, r=0.33) were linear and significant respectively with both FBS and HbA1c.

Discussion

Chronic inflammation contributes to the diabetes pathogenesis and its complications. Joint action of oxidative stress and inflammatory responses induced by hyperglycemia supports the development of atherosclerosis. In our study we observed significantly high FBS and HbA1c in hyperglycemic patients (pre-diabetic and diabetic) compared to controls. Our result was consistent with that of Shrestha S *et al* [11] and Birader SB *et al* [12].

In this study, we also evaluated the levels of inflammatory biomarkers like adiponectin, uric acid, CRP, IL-6 and fibrinogen, all of which are the important mediators of diabetic CV risks. Adiponectin (adipokine from adipocyte) is anti-inflammatory and anti-atherogenic in nature. Increase in its concentration protects from diabetes and CVD. This study demonstrated significant reduction in adiponectin level in pre-diabetic and diabetic participants when compared with control group. Similar observation was documented in the study of Shrestha S *et al* [11], Pauer J *et al* [13] and Jiang Y *et al* [14].

IL-6 is a pro-inflammatory cytokine while CRP is a pentameric acute phase molecule and commonly studied inflammatory marker. IL-6 promotes hepatic synthesis of CRP in response to inflammation. Unlike adiponectin, the levels of IL-6 and CRP showed significant increase from control to pre-diabetic to diabetic patients. Previous studies in support of our study included that of Pradhan AD *et al* [15] and Rasheed MK *et al* [16] who respectively elucidated elevated CRP and IL-6 in diabetic subjects.

Similarly fibrinogen, another acute phase molecule, is an inflammatory mediator of diabetic vascular diseases while uric acid, a purine catabolic end product, that act as both anti-oxidant and oxidant depending upon the physiological stress, also plays crucial role in diabetes and its complications. The levels of both these mediators were high in our patients groups (pre-diabetes and diabetes) compared to control and the difference was significant statistically. Our documentation was in accordance with the studies of James JS *et al* [17], Kafle DR *et al* [18] and Srikanth S *et al* [19].

We observed significant association of HbA1c with adiponectin and IL-6 levels in pre-diabetic subjects however such association with FBS could not be reported. Similarly in diabetic subjects both FBS and HbA1c were significantly associated with adiponectin, IL-6, CRP and uric acid but not with fibrinogen. We found significant inverse correlation of adiponectin with FBS and HbA1c in pre-diabetes. Our result was in confirmation with that of Uslu S *et al* [20], Kumpattla S *et al* [21] and Shrestha S *et al* [11] who suggested negative association of adiponectin with glycemic control parameters.

Regarding IL-6, CRP, fibrinogen and uric acid, all these parameters correlated positively with the FBS and HbA1c. Significant correlation of FBS was obtained with fibrinogen and uric acid while that of HbA1c was observed only with IL-6, CRP and fibrinogen in pre-diabetes. Similarly in diabetes, all these parameters correlated significantly with FBS and HbA1c.

Some previous studies that supported our results are available in literature. Elimam H *et al* [22], Sarinnapakorn V *et al* [23], Li CZ *et al* [24] and Khan DA *et al* [25] in their study elucidated significant linear association between HbA1c and CRP. Such strong association was also shown by Gohel MG *et al* [26] in their cross sectional study. Another study commenced in Sudanese participants too demonstrated significant inverse correlation between CRP, FBS and HbA1c [27].

Kuppenholz B *et al* [28] reported significant positive correlation of IL-6 with HbA1c and fibrinogen with FBS and HbA1c. Similarly Malenica M *et al* [29] and Agrawal A *et al* [30] showed positive correlation of IL-6 with FBS and HbA1c. However Dhawale S *et al* [31] could not document such significant relationship between fibrinogen, FBS and HbA1c. With respect to uric acid, Rabari K *et al* [32] documented significant linear correlation with both glycemic parameters while Whitehead P *et al* [33] and Hidayat MF *et al* [34] could document such relation with HbA1c only. All these results confirmed and supported the findings observed in our study.

Conclusion

Diabetes has added an enormous burden to human health therefore; there is a dire of improved knowledge of diabetes pathophysiology and establishment of preventive measures and tools with optimal predictability of future onset of disease. From this study, we can conclude that type 2 diabetes is associated with inflammation that is manifested by decreased level of adiponectin (anti-inflammatory cytokine) and elevated levels of IL-6, fibrinogen, CRP and uric acid (inflammatory molecules). Further we observed significant association of these mediators with FBS and HbA1c suggesting link between glycemic control and inflammation in hyperglycemic (pre-diabetic and diabetic) patients. Thus it is suggested that improvement in glycemic status can reduce inflammatory mechanisms and prevent onset of pre-diabetes, diabetes and associated complication.

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