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Research Article

INFLAMMATORY MARKERS AND THEIR PREDICTIVE ROLE IN PRE-DIABETES AND DIABETES

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ABSTRACT

Background: Prevalence of diabetes has surged rapidly in the last decades. Insulin resistance is the chief contributor of this chronic disease. Inflammation (chronic low grade) is also mediates insulin resistance leading to hyperglycemia. Elevated concentrations of CRP, pro-inflammatory cytokines (IL-6), fibrinogen, Uric acid and decreased level of anti-inflammatory cytokines (adiponectin) are associated with increased risk of diabetes. Thus the purpose of this study was to evaluate the predictive role of these inflammatory mediators on the risk of diabetes development in future.
Method: With total 371 participants (100 controls, 271 patients: 145 pre-diabetic, 126 diabetic), this study was begun at Santosh Medical College and Hospital, Ghaziabad. Blood sample was collected for the estimation of adiponectin, fibrinogen, IL-6, CRP and uric acid. All the parameters were analysed using kit based methods.
Results: Significantly high values of inflammatory mediators (fibrinogen, IL-6, CRP, uric acid) and low values anti-inflammatory mediator (adiponectin) were obtained in pre-diabetic and diabetic patients compared to controls. In pre-diabetic subjects, except uric acid, all other mediators studied served as the potent risk factors as indicated by significant OR values i.e adiponectin (OR=1.97, p =0.0087),), fibrinogen (OR=2.55, p=0.0004), IL-6 (OR=5.49, p <0.0001) and CRP (OR=3.93, p <0.0001. In case of diabetic subjects, all the inflammatory mediators posed significant threat to future diabetes i.e. adiponectin (OR=4.39, p<0.0001), fibrinogen (OR=3.78, p<0.0001, IL-6 (OR= 8.54, p<0.0001), CRP (OR=7.4, p<0.0001), and uric acid (OR=3.21, p=0.0001).
Conclusions: The individuals with higher inflammatory markers are at greater future risk of diabetes.

INTRODUCTION

Globally diabetes mellitus has established itself a major pandemic due to the associated complications that have added a large burden to the prevention of this metabolic disorder. The prevalence of diabetes is increasing very rapidly these years due to changes in living and dietary habits. This epidemic is prevalent throughout the world (East Asia, Africa, Europe and South America), with 1/5th of the incidence only in South-East Asia. The number of people suffering from diabetes is supposed to reach 642 million by 2040 [1, 2]. The current estimate of diabetes prevalence is 8.8% i.e. 78.1 million in South-East Asia of which higher proportion 69.2 million is residing in India and it is predicted to rise to 123 million till 2040 [3].

Diabetes, a metabolic disorder associated with hyperglycemia, proceeds a latent pre-diabetic phase which is an intermediary phase for progression from normoglycemia to hyperglycemia. Like diabetes, the incidence of pre-diabetes is also increasing. A recent survey reported about 314 million individuals in the world are pre-diabetic and by 2025 the figure is supposed to reach 500 million [4]. In India, the recent picture of pre-diabetic incidence is 36.5 million which may end to 65.3 million until 2040 [3]. It is predicted that the annual turnover of pre-diabetic patients to diabetic state is 5-10%. Since pre-diabetic phase is the final gateway to prevent diabetes progression, there is necessity to identify novel interventions (non pharmacologic and pharmacologic) so that development of diabetes and associated complications can be arrested. As pre-diabetes precedes diabetes, there is requirements of screening process, so that the individuals at the risk of diabetes can be identified earlier and life threatening complications especially macrovascular can be prevented with proper management.

American diabetes association has developed diagnostic criteria for pre-diabetes and diabetes as follows [5]:

State	Fasting sugar	Post prandial Sugar	HbA1C
Normal	<100 mg/dl	<140 mg/dl	<5.6%
Pre-Diabetes	100-125 mg/dl	140-199 mg/dl	5.7-6.4%
Diabetes	>126	≥200 mg/dl	>6.5%

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Impaired insulin action (or insulin resistance) is the major cause of altered glucose metabolism in diabetes. Fat and protein metabolisms are also affected due to impairment in signal transduction pathways, glucose transporter proteins and insulin receptors [6]. Dyslipidemia often occurs in hyperglycemic patients and is the major factor for atherosclerotic disorders. Dyslipidemia, hyperinsulinemia and hyperglycemia together can promote inflammatory response causing increase in the level of inflammatory cytokines [7].

Now diabetes is kept under the category of inflammatory disease since it is shown to be associated with markers of subclinical inflammation in previous studies. Several studies have implicated the changes in inflammatory biomarkers even before the onset of diabetes. As for example Grossman V et al [8] showed increased CRP levels in prediabetic patients but they reported minor difference in the level when compared between pre-diabetes and diabetic individuals. Similarly, Tabak AG et al [9] reported elevated IL-6 and IL-18 in diabetes though the difference was not significant between control and pre-diabetes. Thus, if subclinical inflammation is evident in early phase of dysglycemia, it is possible that inflammatory biomarkers may be associated with pre-diabetes development and progression to diabetes. Therefore, this study is conducted to determine the prognostic significance various inflammatory biomarkers like and, UA, CRP, FGN and IL-6, so that our results may be useful in developing novel approaches that specifically block these biomarkers and prevent their unhealthy effects.

MATERIALS AND METHODS

This case control study was conducted in Santosh Medical College and Hospital, involving 371 participants (100 healthy controls, 145 pre-diabetic and 126 diabetic patients). Patients without history of inflammatory disorder, pregnancy and cardiovascular diseases etc that affect the concentrations inflammatory markers were enrolled. After obtaining approval from the ethical board and written consents from each participant, the study was progressed. Age, WHR and BMI of each participant were recorded. Biochemical parameters like fasting sugar, glycosylated haemoglobin (HbA1c), and inflammatory parameters (adiponectin, fibrinogen, CRP, IL-6 and uric acid) were measured in each patient. Fasting sugar was measured by GODPOD method, HbA1c was estimated using ion exchange resin method. Adiponectin and IL-6 were investigated using ELISA while CRP and fibrinogen were quantified by immune-turbidimetric method. Uric acid was analysed by uricase method.

RESULTS

Table 1 and table 2 show the levels of basic parameters and inflammatory markers in three groups viz control pre-diabetes and diabetes.

Table 1 Basic parameter among Control (C), Pre-diabetic (P) and Diabetic groups (D)

Parameter	C	P	D	p(C/P)	p(C/D)	p(P/D)
Age	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	84.53±7.24	116.63±5.15	160.49±40.15	<0.001**	<0.001**	<0.001**
HbA1c	5.05±0.53	5.87±0.44	6.36±0.89	<0.001**	<0.001**	<0.001**

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

Table 2 Markers of inflammation in Control (C), Pre-diabetic (P) and Diabetic groups (D)

Parameters	C	P	D	p(C/P)	p(C/D)	p(P/D)
Adiponectin	9.01±2.82	8.15±1.87	6.84±1.98	<0.001**	<0.001**	0.04*
CRP	2.81±1.13	4.17±1.36	5.15±1.73	<0.001**	<0.001**	<0.001**
IL-6	4.31±1.8	5.87±1.6	7.51±2.25	<0.001**	<0.001**	<0.001**
Fibrinogen	331.18±58.61	346.58±55.78	369.6±61.38	0.03*	<0.001**	0.001**
Uric acid	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

The median values of adiponectin (anti-inflammatory), CRP, Uric acid, IL-6 and fibrinogen in healthy controls are shown in table 3. The values of CRP, Uric acid, IL-6 and fibrinogen higher than the median, and the values of adiponectin lower than median were considered risk factors of pre-diabetes and diabetes. Table 4 and table 5 show the odds ratios and p value of the various risk factors pre-mentioned in both the patient groups.

Table 3 Median values of inflammatory markers in healthy controls

Parameter	Median
Adiponectin	8.8
CRP	3.11
IL_6	3.99
Fibrinogen	317
Uric acid	4.4

Table 4 Odds ratio and 95% CI (confidence interval) for inflammatory markers in pre-diabetes

Parameter	Odds ratio (OR)	95% CI	p
Adiponectin	1.97	1.19-3.27	0.0087**
CRP	3.93	2.26-6.83	<0.0001**
IL-6	5.49	3.06-9.86	<0.0001**
Fibrinogen	2.55	1.52-4.29	0.0004**
Uric acid	0.89	0.54-1.48	0.6611

Statistically significant: **→p<0.01

Table 5 Odds ratio and 95% CI (confidence interval) for inflammatory markers in diabetes

Parameter	Odds ratio (OR)	95% CI	p
Adiponectin	4.39	2.49-7.74	<0.0001**
CRP	7.4	3.84-14.26	<0.0001**
IL-6	8.54	4.32-16.89	<0.0001**
Fibrinogen	3.78	2.14-6.66	<0.0001**
Uric acid	3.21	1.81-5.68	0.0001**

Statistically significant:**→p<0.01

Of the various inflammatory risk factors assessed adiponectin (odds ratio=1.97, p =0.0087), CRP (odds ratio=3.93, p <0.0001), IL-6 (odds ratio=5.49, p <0.0001) and fibrinogen (odds ratio=2.55, p=0.0004) were found have potent risk of pre-diabetes while in case of diabetes, all the assessed inflammatory risk factors adiponectin (odds ratio=4.39, p<0.0001), CRP (odds ratio=7.4, p<0.0001), IL-6 (odds ratio= 8.54, p<0.0001), fibrinogen (odds ratio=3.78, p<0.0001) and uric acid (odds ratio=3.21, p=0.0001) were shown to have significant risks of diabetes development. Further, on application of multivariate analysis, similar results as in case of univariate analysis were observed i.e. risk potential of the mediators was not affected.

DISCUSSION

In this study, we tried to establish whether changes in inflammatory biomarkers are evident in hyperglycemic state and measurement of inflammatory and anti-inflammatory cytokines could predict onset of diabetes earlier. Inflammation

may be acute or chronic. Chronic inflammation can be further grouped as high grade inflammation and low grade inflammation. Acute inflammation thrives pathogen killing, tissue repair and restores homeostasis following infection and tissue damage, thus making it essential mechanism for survival [13]. On failure of regulatory process of inflammation the host tissue is damaged resulting in chronic inflammation. Chronic inflammation is considered high grade when there are overt clinical manifestations (e.g. rheumatoid arthritis) while it is called low grade when there is absence or minimal manifestation of clinical symptoms. Low grade inflammation exhibits slight elevation in level of cytokines, acute phase proteins and endothelial activators (also observed in acute inflammation) [14].

Previous studies have implicated adipose tissue to be a major contributor to low grade inflammation. Adipose tissue dysfunction impairs lipolysis causing ectopic accumulation of fat and leads to insulin resistance. Adipose tissue besides acting as a fat depot also serves as an endocrine organ and secretes numerous pro-inflammatory and anti-inflammatory cytokines. Hence abnormal functioning of adipose tissue thus plays chief role in initiation of chronic inflammation in which there is increased production of pro-inflammatory (IL-6, TNF, CRP) and decreased production of anti-inflammatory mediators (adiponectin) [15].

Not only adipocytes, hyperglycemia also induces low grade inflammation via production of reactive oxygen species that further stimulate production of IL-6 and TNF-α [16]. Inflammatory markers stimulate insulin resistance by several mechanisms as

- Hindering signaling cascade of insulin
- Impairing action of insulin receptors substrate and glucose transport proteins
- Suppression of adiponectin gene
- Stimulation of IL-6 and TNF-α genes (pro-inflammatory genes) [17].

Pro-inflammatory mediators stimulate NF-kB, a central regulator of inflammation that further promotes transcription of inflammatory genes [18]. On the support of these mechanisms, several previous studies have reported increased levels of markers like TNF-α, CRP and IL-6 in diabetes. Such studies have also been reported frequent association of pre-diabetes with chronic inflammation. Further some cohort studies have demonstrated that genetic polymorphisms in genes of inflammatory mediators (adiponectin, CRP, TNF-r, IL-6) are related with high risk of diabetes. In this study we also found inflammatory mediators to be potent risk factors of diabetes, as indicated by significant OR values.

In our study we found low level on anti-inflammatory (adiponectin) and high level of pro-informatory mediators (IL-6, CRP, FGN and UA) in pre-diabetic patients compared to controls. The levels were further elevated in case of diabetic patients. A similar observation was also provided by Gupta S et al [10]. Likewise Spranger et al [11] demonstrated the association of TNF-α and IL-6 with future diabetes. Additionally another study conducted by Pradhan AD et al [12] also documented association of elevated IL-6 and CRP with the future risk of diabetes development. The association was significant even after the adjustment of BMI, smoking, family history, exercise and alcohol use.

Adiponectin (protein having 244 amino acids) is associated with improved insulin sensitivity and glycemic control, decreased inflammation and preferable lipid profile. In a meta-analysis study with 14,598 participants and 2623 diabetic patients, adiponectin was inversely associated with diabetes risk. The relative risk of 0.72 was recorded for every 1-log μg/mL increase in adiponectin [19]. Similarly in another study, significant association of adiponectin with diabetes was observed (OR=0.88, 95% confidence interval=0.80–0.96) [20]. Biswas D etal reported significant odds ratio of 3.975 (1.312-10.983) indicating positive association of diabetes with genetic polymorphism in adiponectin gene (SNP45T/G) [21].

The pro-inflammatory cytokine involved in insulin resistance is IL-6 and thus is a suitable indicator to predict onset of diabetes [22]. IL-6 mediates inflammatory response and insulin resistance via activation of JAK-2/STAT-3 pathway [23]. CRP is another sensitive biomarker of subclinical inflammation. Previous studies supported our findings as they also reported the strong association of CRP with pre-diabetes and diabetes [[24]. Yatagai T etal demonstrated that treatment of diabetic patients with insulin sensitizers can reduce CRP levels [25]. Sabanayagam C etal documented the OR of 1.31 and 2.17 respectively in pre-diabetic patients with CRP levels ≤mg/L and >3 mg/L thereby indicating strong association between pre-diabetes risk and CRP [26]. Increase in CRP level is also mediated by IL-6. Experimental studies have suggested IL-6 and CRP to be the more sensitive biomarkers of systemic inflammation linked with hyperglycemia. [27]. As per Pradhan AD etal, the relative risks of diabetes were 7.5 for IL-6 and 15.7 for CRP respectively among the women in whom highest versus lowest quartiles of IL-6 and CRP were compared [12].

Fibrinogen is a plasma protein as well as an inflammatory marker having important role in atherosclerotic vascular diseases induced by hyperglycemia. .Though the mechanism still lacks full understanding, fibrinogen is reported to involve in atherosclerosis progression from initial stage (plaque formation) to the thrombus formation and rupture of plaque that ultimately precipitates myocardial infarction [28].

High levels of uric acid are also associated with diabetes development. The prospective Framingham Heart Study conducted in two generations reported that the risk of diabetes increases by 20% (first cohort) and 15% (second cohort) for every 1 mg/dl rise in uric acid level [29]. Similarly, Rancho Bernardo Study (566 participants) observed increase in diabetes risk by 65% per mg/dl increase in uric acid [30]. Likewise, the Rotterdam study, showed that the relative risk of diabetes was 1.68 times greater in the individuals with high uric acid quartile (>6.2 mg/dL) compared to those with low quartile values (≤4.5 mg/dL) [31]. Though still a matter of debate, hyperuricemia is speculated to cause endothelial impairment and decrease in nitric oxide which may contribute to insulin resistance and finally diabetes [32]. Taking these observations together, it is noteworthy to implicate that diabetes development is preceded by chronic inflammation of low grade and the inflammatory biomarkers may have the predictive role in this clinical disorder.

CONCLUSION

In conclusion, the results of our study show that systemic inflammation precedes the development of pre-diabetes and diabetes, thus acting as significant risk factors to these diseases. The individuals with low serum adiponectin and high

serum fibrinogen, IL-6, CRP and uric acid are at increased risk of diabetes in future, however these findings should be further confirmed by the studies having large sample size. Though this study was conducted on a small sample, it can serve as an initiate to future detailed studies in this regard.

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