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Original Research Article

A study on the lipid ratios and inflammatory markers in pre-diabetic and diabetic patients

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ABSTRACT

Background: One of the leading causes of diabetic mortality is cardiovascular disease. Diabetes progression is preceded by pre-diabetic phase which is also at higher cardiovascular risk. Both hyperglycemia and atherosclerotic processes are inflammatory phenomenon. Keeping this in view, it was aimed to evaluate atherogenic indices and correlate them with inflammatory mediators.
Methods: This study included 80 controls, 80 pre-diabetic and 80 diabetic patients. Anthropometric parameters (BMI, WHR) and blood parameters like fasting glucose, HbA1c, lipid profile (cholesterol, HDL, LDL TG, VLDL), adiponectin, IL-6, CRP, fibrinogen and uric acid were analysed.
Results: Significantly high atherogenic indices were observed in pre-diabetic and diabetic subjects compared to healthy controls. The indices were also significantly correlated with BMI, fasting sugar, HbA1c, cholesterol, HDL, TG and LDL. The correlation with HDL was negative and with other parameters, the correlation was positive. In pre-diabetic patients, adiponectin showed significant negative correlation while fibrinogen and CRP showed significant positive correlation with cardiac risk indices. IL-6 was positively correlated only with AIP while correlation of uric acid with these indices was insignificant. In case of diabetic patients, the cardiac risk indices were significantly correlated with adiponectin, IL-6, CRP, fibrinogen and uric acid. The correlation with adiponectin was negative.
Conclusions: The altered atherogenic indices and their significant association with inflammatory markers signify the direct association of inflammation with CVD risks. Thus, there is requirement of novel approaches that can retard inflammatory responses and arrest unwanted cardiac health outcomes.

Keywords: Atherogenic indices/cardiac risk indices, Diabetes, Inflammation, Pre-diabetes

INTRODUCTION

Diabetes mellitus has become a pandemic globally with the worldwide prevalence of 8.3% in 2013 which is predicted to peak at 10.1% by 2035 with almost 80% incidence only in developing nations. Diabetes incidence in India is surging rapidly thus making it a diabetic capital. The incidence of diabetes ranges between 9-12% in different cities of India with nationwide prevalence of 7.7%.[1] With regards to pathogenesis and history of diabetes progression it is evident that individuals before developing overt diabetes undergo a prolonged latent phase known as pre-diabetic phase that confers highest risk for diabetes.[2] It can be defined as the glycemic state higher than the normal level but below than that required for diabetes diagnosis.[3] ADA, (American diabetic association) has set up the diagnostic criteria of pre-diabetes and diabetes as follows: [4]

Table 1: Diagnostic criteria of pre-diabetes and Diabetes.

Pre-diabetes	**Fasting glucose: 100-125 mg/dL**	**Post Prandial glucose: 140-199 mg/dL**	**HbA1c: 5.7-6.4%**
Diabetes	Fasting glucose: ≥126 mg/dL	Post Prandial glucose: ≥200mg/dL	HbA1c: >6.4 %

According to several reports, pre-diabetic phase is the last step to prevent the diabetes progression via lifestyle modification or treatment. Proper management not only impedes the diabetes onset by ≥10 years, but also prevents the disease development.[5] The incidence of pre-diabetes globally is 8% while in India it ranges between 10-14%. If not managed at earlier stage, it is reported that 70% of pre-diabetic patients end to diabetes development with annual turnover of 5-10%.[6]

Both pre-diabetes and diabetes act as major risk factors for CVDs (Cardiovascular diseases). CVD contributes to almost 70% of mortality in the patients with diabetes. It is also documented that the risk of cardiovascular mortality increases by 2-4 times in diabetic patients compared to healthy controls.[7]

Both pre-diabetes and diabetes are associated with dyslipidemia (pro-atherogenic lipid profile) that is characterized by increased concentration of total cholesterol, LDL (low density lipoprotein), TG (triglyceride) and decreased concentration of HDL (high density lipoprotein). This contributes to atherovascular events and increases the likelihood of CVD in future.[8] Early assessment of CVD risks in diabetic patients can aid in lowering CV mortality and improving prognosis of diabetic patients.

Taking this into consideration, continuous efforts are being made to identify new and easily approachable techniques so as to improve cardiovascular health in pre-diabetic and diabetic patients and reduce the rate of mortality. On this regard various atherogenic indices have been devised from the parameters of lipid profile in order to optimise the predictive capability of CV risks. Further, these indices not only reflect the clear picture of both metabolic and clinical interactions between different lipid fractions but also overcome the difficulty encountered on those risk factors that are not easily accessible on routine basis e.g. apo-lipoprotein B.[9]

To mention the names of those indices, important ones are Cardiac risk ratio or Casteli's risk index-I (CRR or CRI-I) which is the ratio of total cholesterol to HDL, Atherogenic index (AI) which is LDL to HDL ratio, Atherogenic coefficient (AC) that is a ratio of non HDL cholesterol to HDL and is the measure of entire atherogenic lipoprotein fraction of plasma, and Atherogenic index of plasma (AIP) which is log of ratio of TG to HDL.[10]

Further, inflammation is the main phenomenon that leads to hyperglycemia and associated complications especially atherosclerosis. Also, there is paucity of studies showing the association of atherogenic indices with inflammatory markers especially in Indian scenario. Thus, in this study it was aimed to assess the atherogenic indices and determine their association with marker of inflammation like adiponectin, CRP, IL-6, fibrinogen and uric acid in pre-diabetic and diabetic patients.

METHODS

With the foresaid aim, 80 controls, 80 pre-diabetic patients and 80 diabetic patients were enrolled in this study conducted at department of Biochemistry, Santosh Medical College and Hospital. The study was conducted from January 2016-April 2019.

Inclusion criteria

Patients with pre-diabetes and type 2 diabetes

Exclusion criteria

Patients with type 1 diabetes, cardiac diseases, pulmonary diseases, renal diseases, hepatic diseases, malignancies, gout and arthritis, and any other conditions that may alter the levels of inflammatory markers were excluded.

Prior to the commencement, the ethical approval and written consent were taken from institutional ethical board and each participant respectively. Basic details of each participant (age, gender, BMI i.e. body mass index) were recorded. Fasting blood sample was collected for quantification of fasting sugar, lipid profile (cholesterol, HDL, triglyceride) and inflammatory markers (adiponectin, CRP, fibrinogen, IL-6 and uric acid).

Serum after separation was stored at -80ºC till analysis. Glycosylated haemoglobin (HbA1c) was assayed in the whole blood. Standard kit based methods were used for the estimation of biochemical parameters as follows:

- Fasting blood sugar (FBS): Glucose oxidase peroxidase (GODPOD) method
- HbA1c: Ion exchange resin method
- Cholesterol (CHO): Cholesterol oxidase peroxidase (CHODPOD) method
- HDL: CHOD-POD/phosphotungustic acid method
- Triglyceride (TG): GPO-PAP method
- Uric acid (UA): Caraway's method
- CRP and Fibrinogen (FGN): Immunoturbidimetric method
- IL-6 and Adiponectin (ADN): Enzyme linked immunosorbent assay.

Level of LDL was computed from Friedwald's equation [11] i.e. LDL=Total Cholesterol-(HDL+VLDL) where VLDL=TG/5

Calculation of cardiac risk indices/atherogenic indices was done as:[12]

$$\text{Castelli's risk index I (CRI - I)} = \frac{\text{Total Cholesterol}}{\text{HDL}}$$

$$\text{Castelli's risk index II (CCR II) or Atherogenic index (AI)} = \frac{\text{LDL}}{\text{HDL}}$$

$$\text{Atherogenic coefficient (AC)} = \frac{\text{Total cholesterol} - \text{HDL}}{\text{HDL}}$$

$$\text{Atherogenic index of plasma (AIP)} = \text{Log}\frac{\text{TG}}{\text{HDL}}$$

Statistical analysis

The data was analysed using ANOVA and post hoc t-test. The association of atherogenic indices with inflammatory markers was determined by Pearson's correlation coefficient.

The difference in level and association was considered statistically significant if $p<0.05$ was obtained.

RESULTS

The result of ANOVA was statistically significant for all the studied variables ($p<0.05$). The comparison between the groups was done by post hoc t test (Figures 1-17).

The age of the control group was significantly lower compared to pre-diabetic and diabetic subjects; however, the age of pre-diabetic and diabetic subjects was similar (Figures. 1).

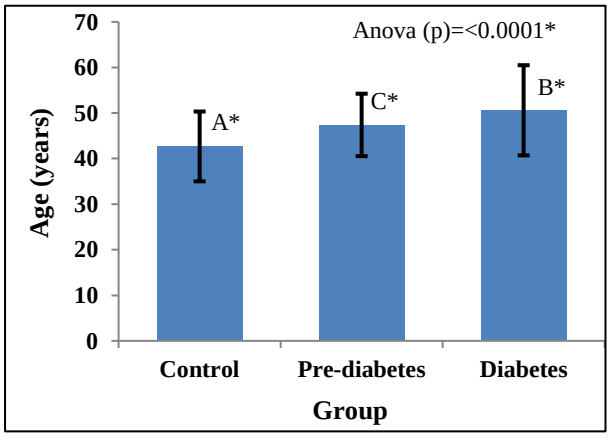

Figure 1: Comparison of age among the study groups.

In case of BMI, diabetic subjects had significantly high BMI compared to control group (Figure 2). Similarly, both fasting blood sugar and HbA1c showed sequential increase from control group to pre-diabetic group and then to diabetic group. The difference of mean was significant in each group comparisons (Figures 3-4).

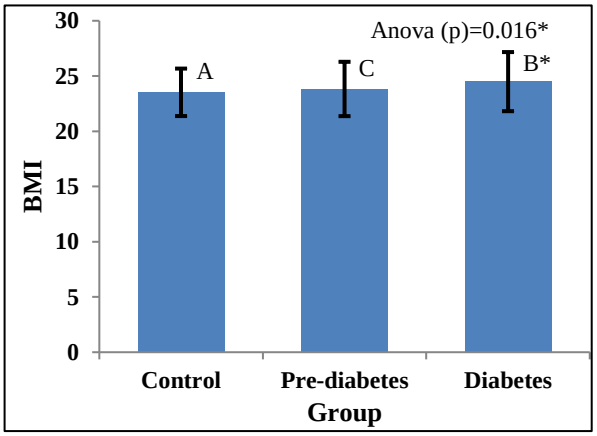

Figure 2: Comparison of BMI among the study groups.

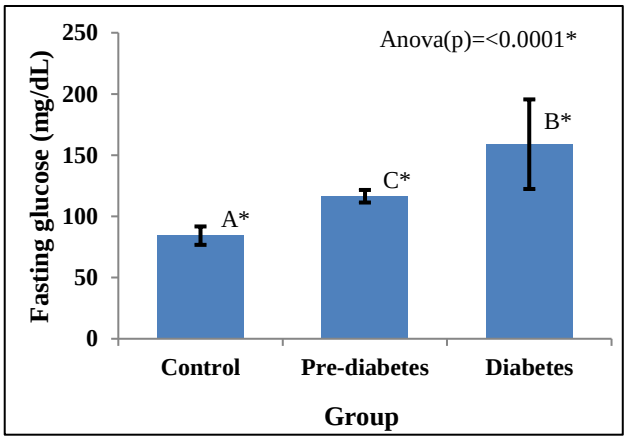

Figure 3: Comparison of FBS among the study groups.

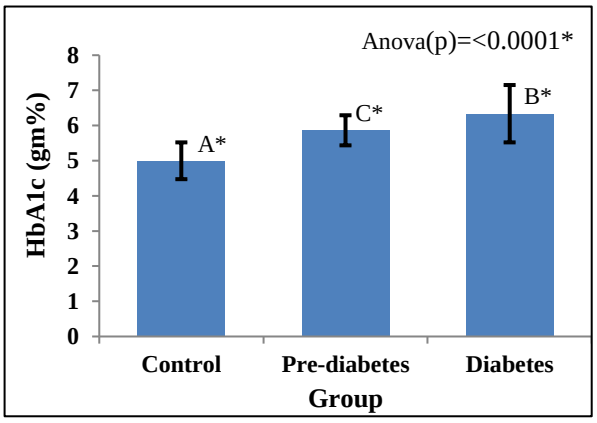

Figure 4: Comparison of HbA1c among the study groups.

Further pre-diabetic and diabetic patients had significantly high cholesterol (Figures 5) and LDL (Figures 8) levels compared to control group while in

case of HDL, the levels was significantly low in diabetic group compared to control and pre-diabetic groups (Figures 6). The level of TG was high in diabetic patients compared to control and pre-diabetic groups, but the significant result was not found in case of control versus pre-diabetic comparison (Figure 7). Both pre-diabetic and diabetic patients had significantly high cardiac risk indices compared to controls. The indices were further significantly increased in diabetic individuals when comparison was made between pre-diabetic and diabetic patients, but the level of statistical significance could not be established between pre-diabetes versus diabetes (in case of AI) and control versus pre-diabetes comparisons (in case of AC) (Figures. 9-12).

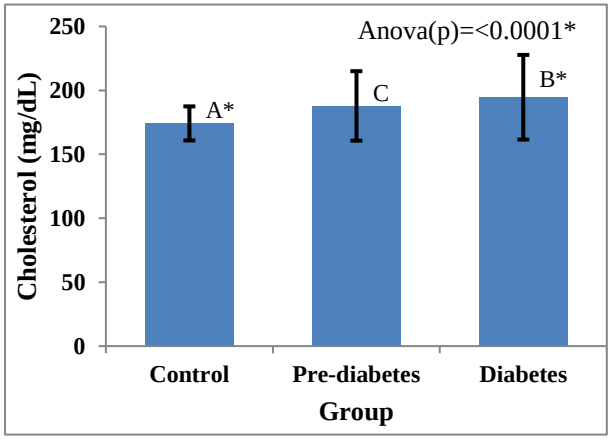

Figure 5: Comparison of CHO among the study groups.

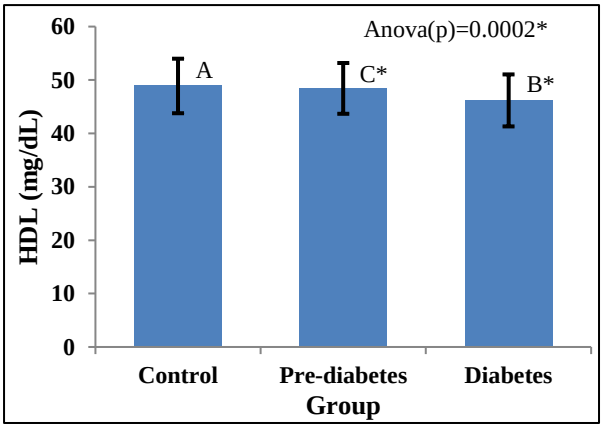

Figure 6: Comparison of HDL among the study groups.

The level of adiponectin was high in control group compared to patient groups, but the significant result was seen only in case of control versus diabetes and pre-diabetes versus diabetes groups (Figure13).

The concentrations of CRP and IL-6 were significantly high in both pre-diabetes and diabetes compared to controls. The levels were further higher in diabetes (pre-diabetes vs diabetes) (Figures. 15-16). Similar was the case with fibrinogen and uric acid but the significant results were not observed in these parameters when compared between control and pre-diabetes groups. (Figure 16-17).

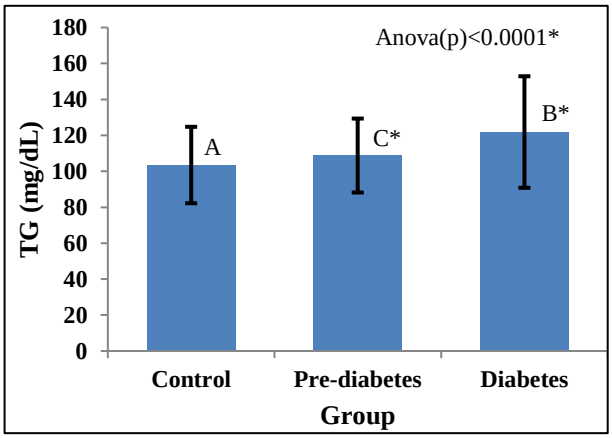

Figure 7: Comparison of TG among the study groups.

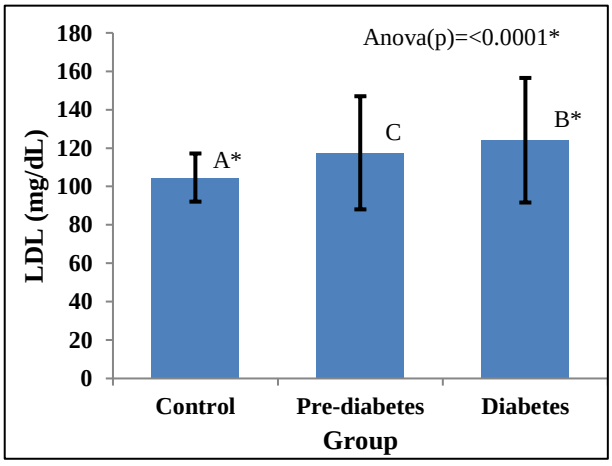

Figure 8: Comparison of LDL among the study groups.

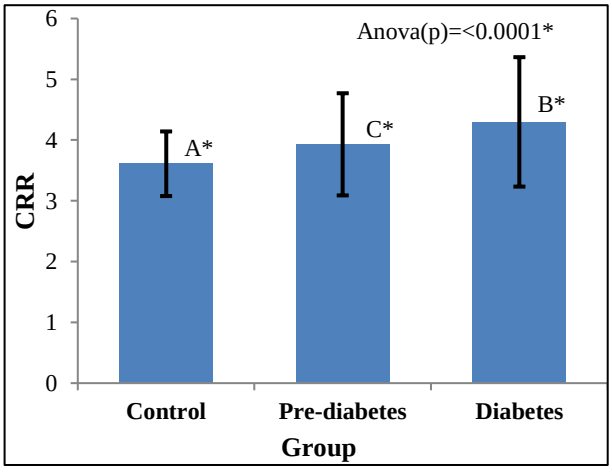

Figure 9: Comparison of CRR among the study groups.

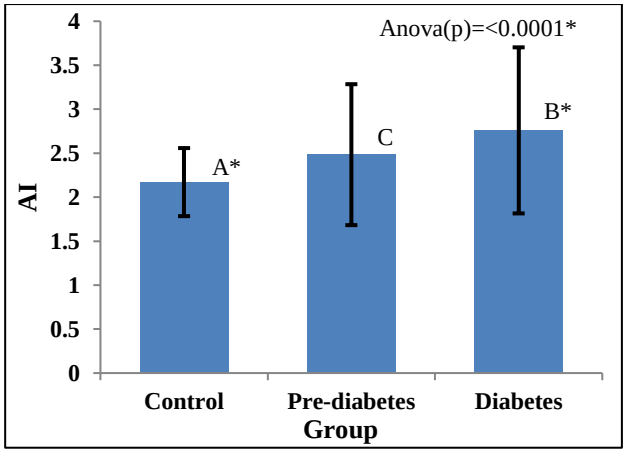

Figure 10: Comparison of AI among the study groups.

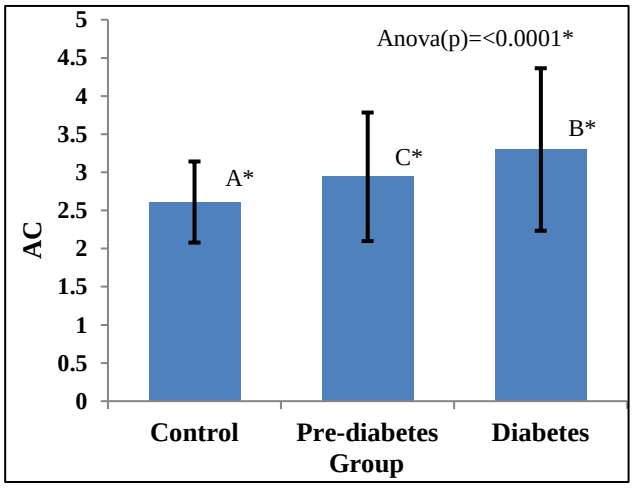

Figure 11: Comparison of AC among the study groups.

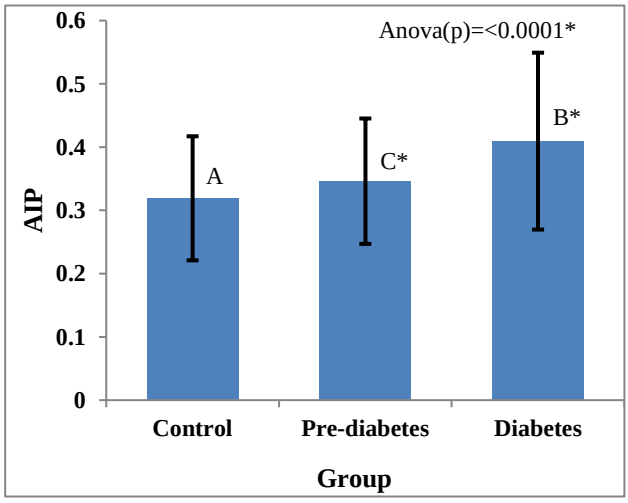

Figure 12: Comparison of AIP among the study groups.

The Table 2 shows the correlation of cardiac indices (CRR, AI, AC, AIP) with basic parameters in pre-diabetic and diabetic individuals.

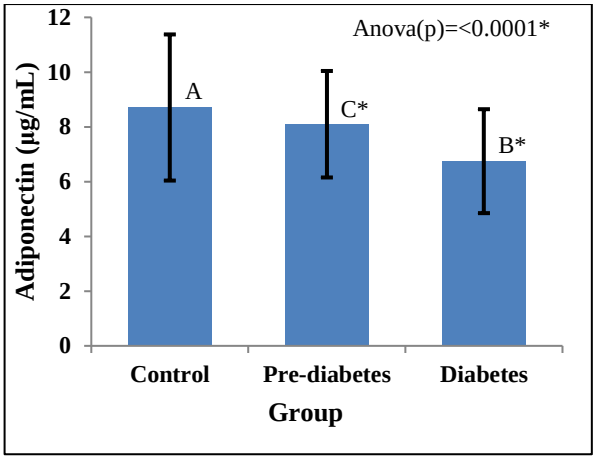

Figure 13: Comparison of ADN among the study groups.

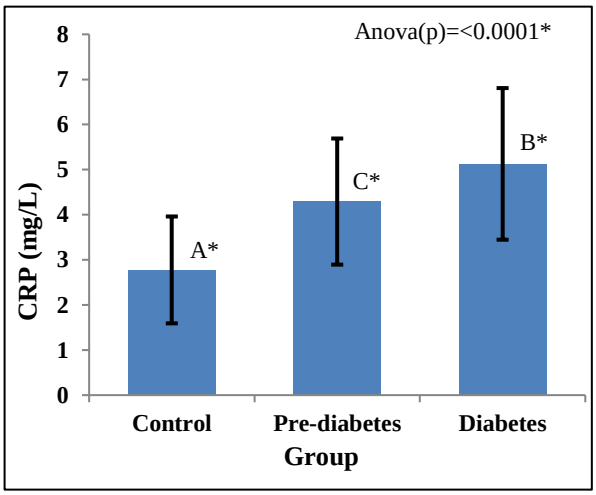

Figure 14: Comparison of CRP among the study groups.

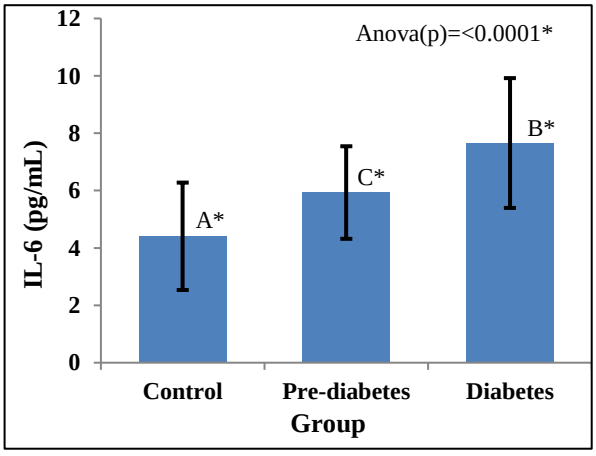

Figure 15: Comparison of IL-6 among the study groups.

Similarly, in Table 3 and Table 4 the correlation of cardiac risk indices with inflammatory markers was shown.

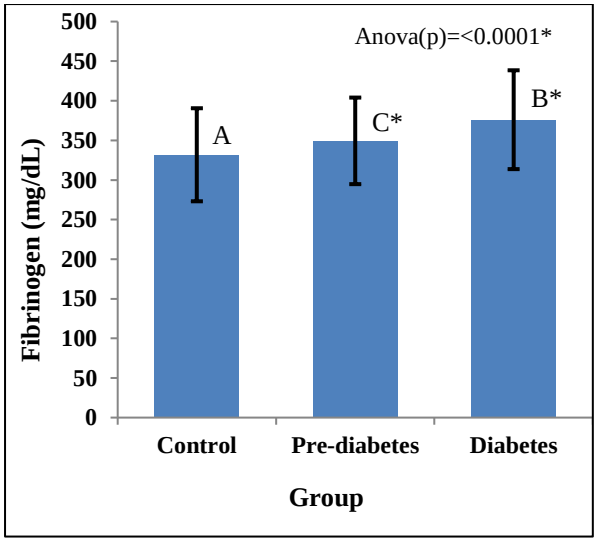

Figure 16: Comparison of FGN among the study groups.

In pre-diabetic patients, adiponectin showed significant inverse correlation while CRP and fibrinogen showed significant linear association with the cardiac risk indices. IL-6 demonstrated significant positive correlation only with AIP while for uric acid authors could not demonstrate any significant association.

Among diabetic patients, significant negative correlation was observed between the cardiac risk indices and adiponectin while for IL-6, CRP, fibrinogen and uric acid the correlation was significantly positive.

In figures 1-17:

A→Comparison between Control and Pre-diabetes
B→Comparison between Control and Diabetes
C→Comparison between Pre-diabetes and Diabetes
*→Statistically significant

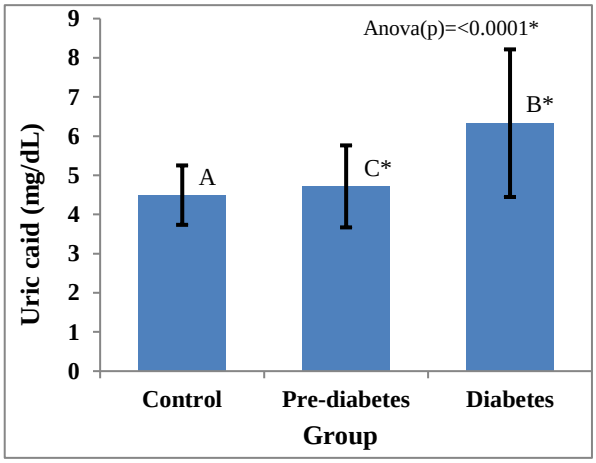

Figure 17: Comparison of UA among the study groups.

DISCUSSION

Diabetes is associated with CVD which is the main cause of mortality in these patients. Therefore, earlier detection of cardiovascular risk in diabetic patients can reduce the CVD associated mortality rate. Several techniques have been developed to predict the cardiovascular risk in diabetic patients.

Table 2: Correlation of cardiac risk indices with basic parameters in pre-diabetic and diabetic groups

Parameters	Pre-diabetes				Diabetes			
	CRR	AI	AC	AIP	CRR	AI	AC	AIP
Age	0.13	0.11	0.15	0.12	0.06	0.04	0.06	0.25**
BMI	0.25**	0.25**	0.26**	0.16	0.28**	0.22*	0.26**	0.41**
Glucose	0.21*	0.17*	0.19*	0.31**	0.37**	0.33**	0.37**	0.28**
HbA1c	0.18*	0.16	0.18*	0.29**	0.45**	0.43**	0.45**	0.30**
CHO	0.91**	0.90**	0.91**	0.24**	0.93**	0.93**	0.93**	0.49**
HDL	-0.78**	-0.72**	-0.78**	-0.6**	-0.74**	-0.7**	-0.74**	-0.60**
TG	0.11	0.02	0.11	0.9**	0.5**	0.36**	0.5**	0.93**
LDL	0.93**	0.95**	0.93**	0.18*	0.92**	0.96**	0.92**	0.39**

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

Table 3: Correlation of cardiac risk indices with inflammatory markers in pre-diabetic group.

Parameter	Adiponectin (r)	CRP (r)	IL-6 (r)	Fibrinogen (r)	Uric acid (r)
CRR	-0.32**	0.24**	0.09	0.25**	0.11
AI	-0.29**	0.20**	0.04	0.26**	0.15
AC	-0.30**	0.27**	0.16	0.38**	0.13
AIP	-0.29**	0.19*	0.34**	0.2*	0.09

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

Table 4: Correlation of cardiac risk indices with inflammatory markers in diabetic group.

Parameter	Adiponectin (r)	CRP (r)	IL-6 (r)	Fibrinogen (r)	Uric acid (r)
CRR	-0.48**	0.71**	0.46**	0.31**	0.29**
AI	-0.42**	0.65**	0.43**	0.33**	0.27**
AC	-0.45**	0.71**	0.46**	0.33**	0.30**
AIP	-0.55**	0.58**	0.49**	0.20*	0.22*

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

The most authentic and economically reliable measures with high predictive capabilities include atherogenic indices or cardiac risk indices namely CRR, AI, AC and AIP. Not only diabetes but the pre-diabetic patients are also at a greater threat to develop cardiovascular diseases. Thus, in this study the cardiac risk indices among control, pre-diabetic and diabetic groups were assessed.

Compared to control group, the pre-diabetic and diabetic patients had significantly high cardiac risk indices. The indices were further elevated in diabetic patients. Similar to this study, previous studies conducted by Mahat R *et al*, and Ranjit PM *et al*, found significantly high atherogenic indices in pre-diabetic patients.[13,14] In this study, the level of CRR, AI, AC and AIP were 3.92±0.84, 2.48±0.8, 2.61±0.53 and 0.32±0.09 respectively in pre-diabetic patients while for diabetic patients they were respectively 4.29±1.06, 2.76±0.94, 3.31±1.06 and 0.41±0.14. Chakraborty M *et al*, reported higher CRR (i.e.>5), AI (i.e>3.5) and AC values (i.e.>4) in pre-diabetic patients. In case of diabetic patients, the authors reported these values to be >11, >9 and >10 respectively.[4] The reported levels of cardiac risk indices were higher than that observed in this study. In contrast Miyazaki Y *et al*, could not document any significant difference in the level of AI in their study.[15]

In the present study presence of dyslipidemia, a major cause of CVD, in the patients involved was documented. Significantly high values of cholesterol, TG and LDL were observed in the patient groups while the level of HDL was significantly low.

These results were in accordance with the previous studies.[13,16,17] LDL is the chief atherogenic lipoprotein while HDL is an anti-atherogenic lipoprotein. Abnormality in lipid metabolism in hyperglycemic state is induced by insulin resistance. In insulin resistant state there is increased lipolysis causing increased free fatty acid flux from adipose tissue and release of VLDL from hepatocytes which further increases the TG and reduces HDL levels.[18]

Elevation in TG facilitates the increase in small and dense LDL particles that have strong atherogenic potential and increases the risk of atherosclerosis via lipid peroxidation and free radical generation.[19] On the contrary HDL promotes reverse cholesterol transport and exhibit anti-oxidant function due to presence of anti-oxidant enzyme paroxonase. Thus, decreased level of HDL and increased level of LDL and TG are strongly associated with CVD in hyperglycemic patients.

Compared to the individual lipid parameters, cardiac risk indices are considered more specific and sensitive marker of cardiovascular risk prediction. However, Da Luz PL et al, regarded AIP to be the more convenient marker compared to CRR, AI and AC especially for myocardial infarction and stroke.[20] It may be due to positive association of AIP with FERHDL (Fractional esterification rate of HDL) and inverse association with LDL particle size. AIP also acts as surrogate marker of apo-lipoprotein B which is not easily available, and it accurately reflects the status of atherogenic LDL and anti-atherogenic HDL particles.[21] The AIP values observed in this study was significantly high in pre-diabetic and diabetic patients. Similar to this study Regmi P *et al*, and Thiyagajarajan R *et al*, also reported high AIP values in pre-diabetic patients suggesting increased CVD risks in future. According to Miric DJ *et al*, AIP was significantly high in diabetic patients with neuropathy than those who did not have. However, Akdogan M *et al*, could not document such significant difference in AIP among diabetic patients with and without retinopathy.[22-25] Since both hyperglycemia and associated CVD are linked with inflammatory mechanisms, the correlation of atherogenic indices with inflammatory mediators (adiponectin, IL-6, CRP, fibrinogen and uric acid) were also assessed. Adiponectin showed significant negative correlation while CRP and fibrinogen showed significant positive correlation with atherogenic indices in pre-diabetic patients. In this study positive association of IL-6 could be documented only with AIP while in case of uric acid any significant association with the indices could not be documented. With regards to diabetic patients, all the inflammatory mediators were significantly correlated with atherogenic indices. The association was negative with adiponectin and positive with IL-6, CRP, fibrinogen and uric acid.The atherogenic indices were also significantly correlated with basic parameters. The correlation was negative with HDL and positive with other parameters (BMI, fasting sugar, HbA1c, cholesterol, TG and LDL). Zhen Li *et al*, reported significant association of AIP with BMI, WHR, glucose and HbA1c similar to that of Juarez CA *et al*, and Nansseu JRN *et al*, Likewise Nimmanapalli HD *et al*, elucidated significant correlation of CRR, AC and AIP

with age, BMI, fasting sugar, HbA1c and lipid parameters.[11,26-28] Previous studies have also reported significant positive correlation between AIP and uric acid.[29,30]

CONCLUSION

Cardiac risk indices can be generated simply by measuring the level of lipid parameters (total cholesterol, LDL, HDL, VLDL and TG) and they are the most reliable and economic method for screening as they surpass the expensive laboratory methods (like estimation of apolipoproteins). In this study, there was increase in values of cardiac risk indices in pre-diabetic and diabetic patients thereby increasing the susceptibility of CVD in these patients in future. Also, these indices were significantly correlated with the inflammatory mediators like adiponectin (cardio-protective cytokine) and IL-6, CRP, fibrinogen and uric acid (cardiac risk factors).

Hence, it is recommended that screening must be conducted among pre-diabetic and diabetic patients, so that the propensity of future development of CVD can be arrested by encouragement of healthy lifestyle or pharmacotherapy that not only improve cardiac risk factors but also increase the level of cardio-protective molecules and decrease the level of those which thrives cardiovascular risks.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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