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Correlation between Dyslipidemia and Markers of Inflammation in Pre-Diabetic and Diabetic Population

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Abstract

Diabetic mellitus is associated with cardiovascular risks that are further aggravated by the presence of dyslipidemia and alteration in inflammatory pathophysiology. Early management of dyslipidemia and improvement of dearranged inflammatory state aid in prevention of atherogenic cardiovascular complications. Therefore this study was commenced with an aim to determine the possible link between lipid parameters and inflammatory mediators and their role in the development of cardiovascular disease in patients with pre-diabetes and diabetes. With the involvement of 371 participants (100 control, 145 pre-diabetes and 126 diabetes), this study was proceeded at Santosh Medical College. Fasting Glucose, HbA1C, lipid profile and inflammatory mediators were assessed in each participants. We found significantly increased levels of fasting glucose, HbA1C(glycosylated hemoglobin), CHO(cholesterol), TG(triglyceride) and LDL(low density lipoprotein) as the participants progressed from normoglycemia-prediabetes-diabetes while level of HDL(high density lipoprotein) was significantly reduced. Similarly in case of inflammatory mediators, adiponectin showed decreasing trend while CRP, fibrinogen, IL-6 and uric acid showed increasing trend with respect to blood glucose level. We also observed positive association of lipid parameters (CHO, TG, LDL) with CRP, fibrinogen, IL-6 and uric acid while HDL showed negative association. The reverse result was obtained in case of adiponectin. Regarding the level of statistical significance, results were more significant in case of overt diabetes compared to latent pre-diabetes. Since both lipid profile and inflammatory markers are altered in patients with pre-diabetes and diabetes thus increasing the CVD risk, timely improvement in their level can arrest the deleterious health outcomes.

Keywords: Dyslipidemia, Inflammation, Pre-diabetes, Diabetes

Introduction: The composition of the human body especially lipids are the important determinants of diabetic incidences. Diabetes, a metabolic disorder, is presented with lipid derangement also known as diabetic dyslipidemia characterized with triad of increased triglyceride (TG), decreased HDL and increased LDL levels [1]. The abnormal lipid profile in diabetes is due to insulin resistance and inhibition of main enzymes of lipid metabolism. The metabolic pathways affected include

apo-protein production, regulatory mechanisms of cholesterol ester, lipoprotein lipase and metabolic action of insulin [2, 3]. A prodormal phase called pre-diabetic phase precedes diabetes. Pre-diabetic state also shares similar pattern of lipid derangement attributed to obesity, insulin resistance and hyperglycemia. It is also associated with increased cardiovascular risk compared to healthy individuals; however association observed is quite less than the overt diabetes [4].

It is evident from previous studies that dyslipidemia thrives the development of macrovascular complications accounting for 82% of deaths of diabetic patients especially due to stroke and heart disease [5]. With regards to Indian scenario, the prevalence of diabetic dyslipidemia is 77%, 80%, 76.9% and 82.9% respectively in urban Mahashtra, Jharkhand, rural Tamilnadu and rural Chandigarh [6]. As per international guidelines, management of lipid profile (i.e. reducing atherogenic lipid like LDL, VLDL, IDL) and increasing anti-atherogenic lipids (HDL) is recommended to prevent diabetic macrovascular complications [7]. Chronic and low grade inflammation is also associated with diabetic dyslipidemia. Inflammation induces synthesis of various acute phase proteins and pro-inflammatory mediators that contribute to insulin resistance and cardiovascular disease [8]. Although evidences of effects of dyslipidemia on inflammatory mediators are available in literature, there is necessity of more researches in this regards especially in pre-diabetic patients. India is considered diabetes capital and since early management in pre-diabetic phase can revert progression to diabetes, we conducted this study with the main objectives to determine the relationship between various inflammatory mediators and parameters of lipid profile in pre-diabetic and diabetic individuals with the view that early detection and correction in lipid abnormalities and inflammation can arrest the risk of diabetic macrovascular diseases.

Materials and methods: This comparative study involved 3 groups of subjects namely control (100), pre-diabetic (145) and diabetic (126) groups. With the approval from ethical committee of the institute and after getting written consent from each subject, the study was commenced at Biochemistry department of Santosh Medical College, Ghaziabad. Patients with stroke, myocardial infarction, malignancy, inflammatory states and pregnancy were excluded from the study.

The anthropometric variables like height, weight and WC(waist circumference) and HC(hip circumference) were recorded by means of stadiometer and measuring tape for calculation of body mass index (BMI) and waist hip ratio (WHR) respectively. Blood sample was collected from each participant for estimation of fasting glucose, HbA1C, lipid profile (CHO, HDL, TG) and inflammatory mediators (adiponectin, uric acid, CRP, fibrinogen and IL-6)

Lipid parameters, fasting glucose, uric acid, fibrinogen and CRP were estimated by kit based method while adiponectin and IL-6 were analysed by ELISA. The level of LDL and VLDL were calculated from Friedwald's equation [9] as:

LDL= Total Cholesterol- (HDL+VLDL)

VLDL= TG/5

Statistical Analysis: The levels of studied parameters were compared between control, pre-diabetic and diabetic groups by student's t-test. One way Anova was used to assess the mean difference in the level of inflammatory markers based on the level of lipid parameters. The correlations between lipid parameters and inflammatory mediators were determined by Pearson's correlation

coefficient. A p value <0.05 indicated the attainment of statistical significance.

Results: Table 1 shows the comparative analysis of age, anthropometric markers (BMI, WHR), fasting glucose HbA1C and lipid parameters (CHO, HDL, TG, LDL and VLDL). Significantly high levels were obtained in pre-diabetic subjects and diabetic subjects when compared with control subjects except for HDL whose level was significantly low. On comparing among diabetic and pre-diabetic subjects, significantly high values of cholesterol, TG, LDL and VLDL, glucose and HbA1C were obtained while for HDL, it was significantly low in diabetes. Table 2 represented inflammatory mediators among the three study groups. The levels of studied mediators were significantly high in pre-diabetic and diabetic subjects.

Tables 3 to 6 demonstrated association of inflammatory mediators with the lipid parameters in pre-diabetic patients while tables 7-10 elucidated the association in diabetic patients. In case of pre-diabetic patients we did not find any significant difference in the mean values of adiponectin, IL-6, CRP, fibrinogen and uric acid with increasing levels of cholesterol and LDL. However, in case of HDL significant decrease in CRP and IL-6 was observed with increase in HDL whereas these mediators were increased significantly with the increase in TG levels.

In diabetic patients, we observed significant reduction in adiponectin and elevation in IL-6, CRP, fibrinogen and uric acid with the increase in cholesterol level. Reverse was observed in mean values of inflammatory mediators with respect to HDL (i.e. increase in adiponectin and decrease in CRP, IL-6 and fibrinogen).

Similarly, there was also significant difference in mean values of inflammatory mediators with the increase in level of TG and LDL. Adiponectin level gradually decreased while rest mediators showed gradual increase. However statistical significance could be established only in case of adiponectin, IL6, CRP and uric acid with respect to LDL, and adiponectin, IL-6 and CRP with respect to TG.

Tables 3-10 also demonstrate the correlation of inflammatory mediators with lipid parameters in two patients groups (pre diabetic and diabetic). In pre-diabetic patients, we found significant negative correlation of adiponectin with CHO, TG and LDL, significant positive correlation of CRP and fibrinogen with CHO and LDL and significant positive correlation of IL-6 with TG. The correlation of HDL with adiponectin was significantly positive while with IL-6, CRP and fibrinogen, it was significantly negative. In diabetic patients, correlation of adiponectin, IL-6 and CRP was significant with CHO, HDL, TG and LDL; however the correlation was positive between HDL and adiponectin, and negative between CRP, IL-6 and HDL. With respect to fibrinogen significant association was document only in case of CHO (linear), LDL (linear) and HDL (inverse) while with uric acid significant linear relationship was obtained with CHO, TG and LDL.

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

Parameter	Control C	Pre-diabetes (P)	Diabetes (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**

CHO	173.27±13.58	186.64±25.98	195.59±35.68	<0.001**	<0.001**	0.01**
HDL	49±5.18	48.19±4.49	46.12±4.73	0.19	<0.001**	0.004**
TG	105±21.27	110.37±20.96	123.1±37.44	0.04*	<0.001**	<0.001**
LDL	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 adiponectin and other markers of inflammation in Control, Pre-diabetic and Diabetic groups

Parameters	Control C	Pre-diabetes (P)	Diabetes (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

Table 3: Association of inflammatory markers with cholesterol in pre-diabetic patients

Cholesterol	No. of patients	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
150-200	125	8.21±1.88	4.11±1.37	5.89±1.59	344.38±55.46	4.58±1.04
210-270	16	7.81±1.99	4.52±1.31	5.5±1.31	364.91±58.01	5.05±1.02
270-330	4	7.33±0.32	4.53±1.13	6.45±2.55	342.17±58.14	4.82±0.99
ANOVA (p)		0.549	0.458	0.492	0.38	0.212
r		-0.25**	0.24**	0.02	0.18*	0.16

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

Table 4: Association of inflammatory markers with HDL in pre-diabetic patients

HDL	No. of patients	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
30-40	3	6.74±0.74	3.02±2.31	8.33±1.32	401.53±54.33	4.63±1.2
40-50	96	7.97±1.71	4.4±1.32	5.49±1.48	351.51±55.67	4.7±1.05
50-60	44	8.56±2.17	3.78±1.26	5.51±1.66	334.49±53.71	4.49±1.01
60-70	2	9.6±0.03	3.07±1.25	3.84±0.12	293.55±17.6	4.8±0.14
ANOVA (p)		0.114	0.02*	0.003**	0.054	0.734
r		0.31**	-0.19*	-0.22**	-0.31**	-0.06

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

Table 5: Association of inflammatory markers with TG in pre-diabetic patients

Triglyceride	No. of patients	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
50-100	46	8.47±2.25	3.8±1.3	5.26±1.43	340.48±59.69	4.44±0.87
100-150	92	8.04±1.57	4.4±1.32	6.13±1.52	350.45±53.8	4.73±1.13
150-200	7	7.36±2.52	3.43±1.51	6.3±1.51	335.9±58.43	4.67±0.38
ANOVA (p)		0.24	0.015*	0.007**	0.538	0.305
r		-0.19*	0.14	0.26**	0.07	0.09

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

Table 6: Association of inflammatory markers with LDL in pre-diabetic patients

LDL	No. of patients	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid

70-140	126	8.23±0.84	4.11±1.36	5.85±1.58	343.82±54.42	4.6±1.04
140-210	16	7.6±2.15	4.6±1.37	6.06±1.78	370.35±62.1	4.95±1.03
210-280	3	7.41±0.37	4.16±1.04	5.32±1.46	335.86±69.51	4.46±0.85
ANOVA (p)		0.35	0.396	0.743	0.19	0.426
r		-0.25**	0.22**	0.01	0.2*	0.14

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

Table 7: Association of inflammatory markers with cholesterol in diabetic patients

Cholesterol	No. of patients	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
150-210	94	7.32±1.82	4.62±1.44	7.08±2.13	360.18±58.33	6.05±1.77
210-270	26	5.59±1.8	6.19±1.16	8.71±1.7	393.97±60.97	6.79±1.95
270-330	4	6.29±0.04	8.81±0.93	8.43±1.19	398.55±77.22	8.3±1.43
330-390	2	3.87±0.8	9.19±2.36	13.06±2.46	437.45±44.05	9.5±1.41
ANOVA (p)		<0.001**	<0.001**	<0.001**	0.02*	0.002**
r		-0.42**	0.69**	0.46**	0.27**	0.37**

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

Table 8: Association of inflammatory markers with HDL diabetic patients

HDL	No. of patients	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
35-45	53	5.98±1.77	6.11±1.63	8.58±1.9	391.01±59.11	6.67±1.86
45-55	69	7.51±1.93	4.53±1.43	6.81±2.18	355.25±56.63	6.15±1.9
55-65	4	6.54±0.86	3.33±1.68	5.27±1.24	333.5±95.55	4.82±0.84
ANOVA (p)		<0.001**	<0.001**	<0.001**	0.002**	0.08
r		0.32**	-0.5**	-0.34**	-0.29**	-0.09

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

Table 9: Association of inflammatory markers with TG diabetic patients

Triglyceride	No. of patients	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
50-100	36	7.66±2.35	4.13±1.6	6.24±2.07	359.78±62.84	5.96±1.84
100-150	65	6.97±1.46	5.19±1.26	7.66±1.92	370.86±57.45	6.27±1.77
150-200	23	5.27±1.74	6.45±2.04	9.01±2.46	383.09±75.5	6.93±2.19
>200	2	5.86±2.7	7.37±2.15	7.84±1.44	350.35±22.13	7.95±1.06
ANOVA (p)		<0.001**	<0.001**	<0.001**	0.526	0.157
r		-0.44**	0.53**	0.39**	0.12	0.23**

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

Table 10: Association of inflammatory markers with LDL diabetic patients

LDL	No. of patients	Adiponectin	CRP	IL-6	Fibrinogen	Uric acid
50-100	25	7.34±1.46	4.2±1.32	6.29±1.73	349.85±69.25	5.81±1.69
100-150	85	7.02±2.01	5.05±1.48	7.61±2.25	370.24±56.98	6.335±1.88
150-200	11	5.22±1.76	6.38±1.68	8.25±1.22	383.54±63.2	6.39±1.86
>200	5	4.82±1.5	8.92±1.44	10.19±3.06	426.88±60.76	8.7±1.58
ANOVA (p)		0.001**	<0.001**	<0.001**	0.055	0.02*
r		-0.37**	0.65**	0.43**	0.29**	0.34**

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

Discussion: Diabetes mellitus is frequently associated with dyslipidemia depending on duration, severity, glycemic status, nutritional status and other factors. More than 70% of diabetic patients are presented with dyslipidemia. In this study we found high serum cholesterol, TG and LDL in pre-diabetic and diabetic patients. Similar results were also observed in study of Kaithala C *et al* [10]. In accordance to our study, Miyazaki *et al* [11] and Balgi V *et al* [12] also reported high total cholesterol, LDL and TG levels, and significantly low HDL in pre-diabetic patients. Their reports were further confirmed by that of Bazzi *et al* [13] and Kansal *et al* [14]. Study of Mahat R *et al* [15] and Ranjit PM *et al* [16] showed that the lipid ratio such as TC/HDL, LDL/HDL and TG/HDL were also significantly increased in patient group compared to the control group. The increase was more significant in diabetic patients compared to pre-diabetic patients. These results indicated increased CV risks in the diabetic and pre-diabetic patients.

Both carbohydrate and lipid metabolism are interrelated therefore alteration in carbohydrate metabolism can deteriorate lipid metabolism too and vice versa, thus affecting the blood lipid levels. Insulin affects production of apo-lipoprotein and regulates lipoprotein lipase action. Insulin resistance decreases the activity of hepatic lipase and production of active lipoprotein lipase that leads to diabetic dyslipidemia [17]. According to Goldberg *et al*, hyperglycemia stimulates export of cholesterol ester to VLDL particles from HDL causing LDL particles to be laden with a greater proportion of HDL esters and hence leading to decrease in level of HDL [18]. Poor insulinization increases lipolysis in adipocytes with increased production of FFAs (Free fatty acids) that are transported to liver and may further increase the level of VLDL [19]. Dyslipidemia has been recognized as independent cardiovascular risk factor in hyperglycemic patients. When dyslipidemia co-exists with atherosclerosis related inflammatory mechanisms, the risk becomes further profound [20]. In the recent years researches linking metabolism and immune system are occurring at a rapid pace. It has been shown than interrelationship between metabolism and immunity though is proven beneficial under normal physiological state, it can have adverse health effects under the state of metabolic stress.

Anabolic pathways (insulin signaling pathways) are suppressed while catabolic pathways are activated in presence of inflammation that further culminates to insulin resistance and lead to hyperglycemia and dyslipidemia [21]. Pradhan *et al* reported CRP to be the mediator of insulin resistance and diabetes [22]. Similarly Sunny *et al* established significant relationship between CRP and dyslipidemia [23]. Study of Rhee EJ *et al* demonstrated positive correlation between CRP, cholesterol and TG [24]. Keeping the view of these previous reports, we also determined the interrelationship between dyslipidemia and inflammatory mediators using ANOVA. We observed increase in levels of inflammatory mediators (CRP, fibrinogen, IL-6 and uric acid) with the increase in the level of lipid parameters (Cholesterol, TG and LDL) while the level decreased with increase in HDL level in the patients groups. However, the level of adiponectin demonstrated decreasing pattern with the increase in CHO, TG and LDL, and increasing pattern with the increase in HDL. The association between lipid parameters and inflammatory mediators were further confirmed by Pearson's correlation coefficient. We observed positive correlation of adiponectin with HDL and negative correlation with TG, LDL and CHO, and reverse association was observed in case of CRP,

fibrinogen, IL-6 and uric acid. The level of statistical significance was achieved more in case of diabetic patients compared to the pre-diabetic patients. This indicates that CRP, fibrinogen, IL-6 and uric acid are the important inflammatory mediators of macrovascular complications and alteration in their level in the hyperglycemic patients further exacerbates the risk of diabetic vascular disease.

Conclusion

In our study we observed diabetic dyslipidemia in the form of hypertriglyceridemia, hypercholesterolemia and increased LDL levels. We also observed reduction in HDL level, which is the prominent anti-atherogenic lipid. The levels of inflammatory mediators like CRP, fibrinogen, IL-6 and uric acid were increased and anti-inflammatory markers like adiponectin was reduced. We also documented significant association between lipid parameters and inflammatory parameters. Both dyslipidemia and the inflammatory mediators are the important risk factors for the development of diabetic complications especially marcovscular complications. Thus from our study, it is evident that when these two risk factors (inflammatory and dyslipidemia) coexist together the risk of diabetic vascular complications are amplified. Therefore, there is necessity of correcting abnormal lipid profile and inflammation by the means of aggressive life style modification, changes in dietary habits and increase in physical activity followed by pharmacotherapy if needed. Since pre-diabetic phase is the intermediate phase between normoglycemia and hyperglycemia, interventions (both non therapeutic and therapeutic) at this phase can prevent the progression to diabetes and future cardiovascular risks. However further investigations are also recommended to expedite the role of lipid profile and inflammatory markers in assessment of CVD risk and to determine the joint potentially of lipid profile and inflammation to be depicted as early markers of diabetic macrovascular complications.

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