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Atherogenic Predictor Indices: Role in Assessment of Cardiovascular Risk in Type 2 Diabetes Mellitus.

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***Abstract*:** *Dyslipidemia has been identified as one of the most important risk factor associated with cardiovascular diseases (CVD). Absence of abnormal conventional lipid profile may not eliminate the risk of CVD in diabetics. Novel lipid ratios such as atherogenic index of plasma, atherogenic coefficient, castelli risk index I & II and non HDL-C have been found to indicate the level of atherogenicity and hence are suggested to be a better predictor of CVD in diabetes. This cross-sectional study was conducted for 2 months involving 50 diabetic and 50 healthy individuals. Lipid profile and plasma glucose levels were estimated. Using the lipid profile values atherogenic indices such as atherogenic index of plasma (AIP), atherogenic coefficient (AC), castelli risk index I & II (CRI-I, CRI-II) and non HDL-C were calculated. Continuous variables were expressed as mean and SD. Student's t test was used to compare the means of two groups. Pearson's linear correlation was used for evaluating the relationship of plasma glucose levels with traditional lipid parameters and atherogenic lipid indices in T2DM patients. Results were taken to be statistically significant at P ≤0.05. All the lipid profile values in diabetics were higher but only triglycerides (TG) and very low density lipoprotein (VLDL-C) showed statistical significance (p=0.0015 & p= 0.0012 respectively). Similarly, atherogenic indices were higher in diabetic group but only AIP showed statistical significance (p=0.0011). Fasting glucose level showed positive and significant correlation with TG (r=0.2879, p=0.042), VLDL (r= 0.2884, p=0.042) and AIP (r= 0.2961, p=0.036). Total cholesterol (TC) showed a positive and significant correlation with CRI-I (r=0.722, p<0.00001), CRI-II (r=0.718, p<0.00001), AIP (r=0.365, p<0.009), AC (r=0.722, p<0.00001) and non HDL – C (r=0.985, p<0.00001). TG showed positive correlation with all lipid indices except CRI-II. Similarly, Low density lipoprotein (LDL –C) showed statistically significant positive correlation with all the indices except AIP. Additionally, high density lipoprotein (HDL-C) showed negative correlation with all the indices but statistical significance was found only with CRI-I and AC.The study showed derangements in lipid profile among diabetic patients along with abnormally high values of atherogenic index of plasma, indicating its potential use in identifying diabetic patients who are at risk for cardiovascular disease.*

Keywords: *Diabetes Mellitus, Lipid profile, Cardiovascular risk, Atherogenic Index of Plasma, Atherogenic co-efficient, Castelli risk index – I, Castelli risk index – II.*

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I. Introduction

Globally, 422 million adults are living with DM as per 2014 WHO report.[1] The prevalence of DM in India is more than 62 million.[2] Type 2 Diabetes Mellitus (T2DM) is commonly associated with dyslipidemia, hypertension and prothrombotic factors.[3] Dyslipidemia has been identified as one of the most important risk factor associated with CVD[4] and it is the key cause of high morbidity and mortality in DM. The lipid alterations

associated with diabetes are mainly caused by increased influx of free fatty acids secondary to insulin deficiency or resistance.[5]

In the absence of abnormal lipid profile, the risk of CVD cannot be ruled out. Different combinations of traditional lipid parameters can be used to calculate novel atherogenic lipid ratios, which have been found to indicate the level of atherogenic risk, and hence are suggested to be a better predictor of CVD.[6] The commonly calculated lipid ratios are Atherogenic Index of Plasma (AIP), Castelli Risk Index I & II (CRI-I & CRI-II), Atherogenic Coefficient (AC) and non HDL-C. These ratios are simple and can be calculated easily in the clinical practice for assessing the risk of CVD beyond the routinely done lipid profile.

AIP is based on TG and HDL-C, both of which are independent risk factors for CVD[7] and it reflects the relationship between non atherogenic and atherogenic lipoproteins. CRI-I & II are calculated from TC, LDL-C and HDL-C and are more accurate predictors of cardiovascular (CV) risk than traditional lipid parameter.[6] Additionally, Atherogenic Coefficient is one more ratio relying on the significance of HDL-C in predicting the risk of CVD.[8]

In view of the foregoing, the present study was designed to examine the alterations in traditional lipid profile and atherogenic predictor lipid indices and to examine their role in assessing the CV risk in T2DM patients.

II. Materials and methods

A Cross sectional study was conducted in the Department of Biochemistry for a period of 2 months. Fifty clinically diagnosed T2DM patients in the age group 40-65 years and 50 age and sex matched healthy controls were included in the study using convenient sampling technique. Subjects suffering from the previous history of other diseases like Thyroid disorders, Hypertension, Smoking, Pregnancy, Alcoholism etc and patients not willing to participate were excluded.

Ethical clearance was obtained from institutional ethical committee. The purpose and aim of the study was explained to all the study subjects. After obtaining consent from willing participants, detailed information regarding demographic profile, complete clinical history and medical history was collected. Fasting blood sample was used to analyze glucose and lipid profile while, sample collected after 2hrs of meal was used to estimate post prandial plasma glucose levels. Serum TG[9], TC[10] and HDL-C[11] were measured in a fully automated Meril Autoquant 400 analyzer. LDL-C was calculated using Fredrickson Friedwald's formula[12]: (TC-HDL)-TG/5, if TG is < 400 mg/dL and LDL was estimated by direct method where TG >400 mg/dL.

Calculation of Lipid Indices[6]

1. Atherogenic Index of Plasma = log (TG/HDL)
2. Atherogenic Co-efficient = (TC – HDL) / HDL
3. Castelli Risk Index I = TC / HDL
4. Castelli Risk Index II =LDL / HDL
5. Non HDL-C = TC - HDL

Statistical analysis: Data analysis was carried out using the statistical package for social sciences (SPSS) 18.0 software for windows. Continuous variables were expressed as Mean and SD. Student's t test was used to compare the means between two groups. Pearson's linear correlation was used for evaluating the relationship of plasma glucose levels with traditional lipid parameters and atherogenic lipid indices in T2DM patients. Results were taken to be statistically significant at $P \leq 0.05$.

III. Results

A total of fifty diabetic patients were studied to assess the alteration in lipid profile and atherogenic indices and compared with age and sex matched fifty healthy controls.

Table No. 1: Mean age and plasma glucose levels among study participants

Variables	Controls (N=50)		Cases (N=50)		P value
	Mean	SD	Mean	SD	
Age (years)	50.19	8.44	53.20	7.27	0.06
FPG (mg/dL)	94.28	13.82	180.18	91.33	0.0001*
PPPG (mg/dL)	121.78	18.46	285.38	115.57	0.0001*

FPG – fasting plasma glucose, PPPG – postprandial plasma glucose, SD – Standard deviation, * - Statistically significant

The mean age of the diabetic patients was 53.20 ± 7.27 years and controls was 50.19 ± 8.44 years (p=0.06). Both the fasting and postprandial glucose levels were high among diabetic patients when compared to cases and was statistically significant (Table 2)

Table No. 2: Comparison of lipid profile and atherogenic indices between diabetic patients and healthy controls.

Variables	Controls (N=50)		Cases (N=50)		P value
	Mean	SD	Mean	SD	
Traditional lipid profile (mg/dL)					
Total Cholesterol	183.24	33.06	185.96	53.84	0.76
Triglycerides	161.06	70.77	223.5	115.00	0.0015*
High density lipoprotein- Cholesterol	48.74	8.39	46.34	9.52	0.18
Low density lipoprotein – Cholesterol	101.28	25.96	98.84	44.45	0.73
Very low density lipoprotein –Cholesterol	31.74	14.20	44.46	22.90	0.0012*
Atherogenic Indices					
Atherogenic Index of Plasma	0.49	0.17	0.63	0.24	0.0011*
Atherogenic Co-efficient	2.82	0.77	3.09	1.25	0.20
Castelli Risk Index – I	3.82	0.77	4.09	1.25	0.20
Castelli Risk Index – II	2.13	0.62	2.17	1.06	0.82
Non HDL-C	134.50	30.90	139.62	50.42	0.54

*Statistically significant

The serum concentration of lipid profile and atherogenic indices among study participants are represented in Table 2. Even though there was increased total cholesterol, triglycerides, LDL-C and VLDL –C among diabetic patients as compared to healthy controls, only TG and VLDL - C showed statistical significance (p=0.0015, p=0.0012 respectively).

Atherogenic indices like castelli risk index (I & II), atherogenic index of plasma, atherogenic co-efficient and non HDL-C showed increased levels in diabetics than controls. However, only AIP showed statistical significance (p<0.0011).

Table No. 3: Pearson's correlation between plasma glucose levels (both fasting and postprandial) and traditional lipid parameters in diabetic patients

Parameters	Fasting Plasma Glucose		Postprandial Plasma Glucose	
	R value	P value	R value	P value
Total Cholesterol	0.1637	0.255	0.073	0.612
Triglycerides	0.2879	0.042*	0.211	0.1411
High density lipoprotein- Cholesterol	-0.1245	0.388	-0.0443	0.76
Low density lipoprotein – Cholesterol	0.0743	0.608	-0.009	0.950
Very low density lipoprotein – Cholesterol	0.2884	0.042*	0.2128	0.137

*statistically significant

Table No. 4: Pearson's Correlation between plasma glucose levels (both fasting and postprandial) and atherogenic indices in diabetic patients

Parameters	Fasting Plasma Glucose		Postprandial Plasma Glucose	
	R value	P value	R value	P value
Atherogenic Index of Plasma	0.2961	0.036*	0.1895	0.187
Atherogenic Co-efficient	0.2525	0.0768	0.1215	0.4006
Castelli Risk Index-I	0.2525	0.0768	0.1215	0.4006
Castelli Risk Index-II	0.1331	0.3568	0.034	0.810
non HDL	0.1983	0.1674	0.086	0.5498

*statistically significant

The Pearson's correlation between plasma glucose levels and traditional lipid profile and lipid indices in diabetic patients is depicted in table 3 & 4 respectively. Among the diabetic subjects, FPG was positively and significantly correlated with TG (r=0.2879, p=0.042), VLDL (r= 0.2884, p=0.042) and AIP (r= 0.2961, p=0.036) but no significant correlation was demonstrated with other lipid parameters and atherogenic indices. FPG showed negative correlation with HDL-C (r=-0.1245, p=0.38) which was not statistically significant. Further PPPG showed no significant correlation with the traditional lipid parameters and atherogenic indices.

Table No. 5: Pearson's correlation between lipid profile parameters and atherogenic indices in diabetic patients *statistically significant

	CRI-I		CRI-II		AIP		AC		Non HDL-C	
	R value	P value	R value	P value	R value	P value	R value	P value	R value	P value
TC	0.723	0.00001*	0.718	<0.00001*	0.365	0.0091*	0.723	<0.00001*	0.985	<0.00001*
TG	0.374	0.007*	0.133	0.359	0.995	<0.00001*	0.374	0.0074*	0.466	0.0006*
HDL-C	-0.287	0.043*	-0.185	0.199	-0.231	0.1066	-0.287	0.0433*	0.276	0.05*
LDL-C	0.743	<0.00001*	0.867	<0.00001*	0.138	0.3388	0.742	<0.00001*	0.920	<0.00001*
VLDL-C	0.374	0.0074*	0.132	0.3593	0.904	<0.00001*	0.372	0.0074*	0.465	0.0006*

The strengths and directions of correlation between the various lipid profiles and indices of atherogenicity are shown in table 5.Total cholesterol showed a positive and significant correlation with CRI-I (r=0.722, p<0.00001), CRI-II (r=0.718, p<0.00001), AIP (r=0.365, p<0.009), AC(r=0.722, p<0.00001) and non HDL –C (r=0.985, p<0.00001). TG showed positive correlation with all lipid indices except CRI-II. Similarly, LDL –C showed statistically significant positive correlation with all the indices except AIP. HDL-C showed negative correlation with all the indices but statistical significance was found only with CRI-I and AC.

IV. Discussion

The burden of DM is on the rise in all developing countries. The cause of greater relative risk of CVD in diabetes is attributed to adverse changes in cardiovascular risk factors such as HDL-C, TC, TG and LDL-C. Detection and treatment of dyslipidemia in diabetics is one of the major step towards reducing the risk of CVD associated with diabetes.[12] Calculating the ratios using the traditional lipid parameters especially in situations where LDL-C levels are within the optimum range could serve as an indicator of the atherogenicity.[6] The present study examined the alterations in traditional lipid profile and atherogenic lipid indices and their role in assessing the cardiovascular risk in diabetes patients.

In this study the mean value of FBG & PPBG were significantly increased in cases as compared to control group (p<0.0001). Prolonged hyperglycaemia causes generalized vascular endothelial damage resulting in decreased in the activity of lipoprotein lipase leading to high TG and low HDL-C concentration in blood. Results of the present study showed significantly higher concentration of TG and VLDL in diabetic patients (p=0.0015 and p=0.0012). However TC, LDL-C and HDL-C were not significantly different in diabetic patients as compared to healthy controls.

Coronary artery disease is associated with alteration in lipid metabolism which include high TG levels with reduced HDL-C.[13] TG is considered as an independent risk factor in the pathogenesis of coronary artery diseases.[14] Apart from the commonly employed lipid parameter lipid ratios are gaining importance as risk indices in predicting risk of coronary arteriosclerosis and CVD.[6,15] On evaluation of lipid ratios such as AIP, AC, CRI-I, CRI-II and non HDL-C, in the present study it was observed that there was increase in all lipid indices in diabetic group as compared to control group. However, only AIP levels were statistically higher in diabetic as compared to healthy controls (p<0.0011).These findings are in agreement with few other studies.[16,17] Siddiqui IA et al[16] studied the association of lipid indices with micro and macro vascular complication in type 2 DM. Their findings demonstrated significantly higher levels of AIP and CRI - I in diabetes than in controls and both the indices lowered in patients after treatment with insulin.

Lipid ratios such as AC and AIP are found to have a good implication prediction in daily practice to assess CV risk in type 2DM and furthermore AIP has a better predictability in assessing CV risk in type 2DM.[17] Atherogenic Index of Plasma is a ratio calculated as log(TG/HDL-C) and the value predicts the cardiovascular risk in diabetic patients. High levels of TG, VLDL and LDL cholesterol mediate the progression of atherosclerosis.[18,19] In the present study even though the level of HDL-C was not statistically different in both the groups, AIP showed significant difference between diabetes and controls. AIP values reflect the relationship between anti atherogenic and pro atherogenic lipids and hold the role in predicting CV risk in DM patients.[20]AIP was positively correlated with total cholesterol, triglycerides and VLDL-C which was statistically significant. In addition, AIP showed positive correlation with LDL-C & non HDL-C and negative correlation with LDL-C but was not statistically significant.

Atherogenic Co-efficient calculated as non HDL-C/HDL-C is a measure of cholesterol in LDL-C, VLDL-C & IDL-C lipoprotein fractions with respect to good cholesterol or HDL-C. It reflects the atherogenic potential of the entire spectrum of lipoprotein fractions. In the present study, there was increase in the levels of AC in cases (3.09±1.25) compared to controls (2.82±0.77). These findings are in accordance with other studies.[6,17] AC ratio is positively correlated with TC, TG, LDL-C, VLDL-C & non HDL-C which is statistically significant (p <0.00001), which implies that higher the dyslipidemia, high is the risk of developing CVD and vice versa.

Castelli's risk index (CRI) is based on three important lipid profile parameters TC, LDL-C& HDL-C. CRI-I calculated as ratio of TC/HDL-C and CRI-II as the ratio of LDL-C/HDL-C. In the present study both CRI-I& CRI-II were higher in cases compared to controls but no statistical difference was found. Further, CRI-I showed positive correlation with TC, TG, LDL-C, VLDL-C& non HDL-C which was statistically significant but not with HDL-C. CRI-II showed positive correlation with TG, LDL-C& non HDL-C which was statistically significant.

Non HDL-C is calculated as {TC - HDL-C}. It is a single index of all atherogenic apolipoprotein B containing lipoprotein LDL, VLDL, IDL and lipoprotein A. Calculation of non HDL-C is more practical, reliable and inexpensive and is accepted as a surrogate marker of apo B in routine clinical practice.[21] Non HDL-C is easily available with every lipid profile ordered and serves as an index of cardiovascular risk in diabetes mellitus patients in whom LDL-C may not be elevated.

The result of the present study revealed that all the atherogenic indices of cases were higher than those of control. Similar observations were made by other works.[20-22] All the above findings buttress the relevance of these lipid ratios in identifying and assessing the risk for cardiovascular diseases over the use of individual lipids alone and these ratios can be used to predict the CV risk in the absence of abnormality in traditional lipid profile.

V. Limitation

Our study has few limitations, one of which was small sample size. Secondly, information concerning other profound risk factors such as physical activity, diet, genetic factors, anthropometric measurements, etc was not collected. Studies with large sample and multi-centric approach are required to validate the conclusions.

VI. Conclusions

In conclusion, the present study showed derangements in the lipid profile of diabetic patients along with abnormally high values of atherogenic index of plasma. This high atherogenic index of plasma indicates the potential use of it in identifying diabetic patients at higher risk of cardiovascular disease. Along with this AIP, AC and CRI-I showed positive correlation with atherogenic lipid profile. Thus the use of these indices should be encouraged to adjunct the existing profile of tests in effective management of diabetes.

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Conflict of Interest: None

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