Original Article

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Assessment of Atherogenic Indices in Type 2 Diabetes Mellitus

Biochemistry Section

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ABSTRACT

Introduction: Worldwide, Diabetes mellitus is the most common chronic disorder and risk factor for Coronary Artery Disease (CAD). The atherogenic indices including atherogenic index of plasma is a novel indicator of diabetic dyslipidemia, which is equivalent to the risk predictor of CAD.

Aim: To compare the atherogenic indices including atherogenic index of plasma, cardiac risk ratio and atherogenic coefficient in individuals with Type 2 diabetes mellitus and in control group.

Materials and Methods: The present study included 280 participants; of which 70 were healthy age and sex matched controls and 210 were known cases of Type 2 diabetes mellitus (30-60 years). Lipid profile was assessed by enzymatic assay and atherogenic indices including, atherogenic index of plasma, cardiac risk ratio and atherogenic coefficient were calculated. Patients with chronic liver/kidney disease and on lipid lowering drugs were excluded. Statistical analysis was done with SPSS version 20.0 and chi-square and one sample t-test was applied, $p<0.05$ were considered as statistically significant.

Results: Duration of diabetes was 6 to 10 years, the average BMI was 26.09 kg/m^2. Among 210 diabetic patients 73 (34.76%) were of normal weight, 128 (60.95%) overweight and 09 (4.29%) obese; 87% had diabetic dyslipidemia. High level of HbA1c (8.8±1.5%) was associated with increase in duration of diabetes, the average duration of Type 2 diabetes in study population was 9.8±4.4 years. Significantly increased levels of cholesterol (188.3±31.9), triglyceride (161.3±19.4) and LDL-C (114.9±30.9) and decreased HDL-C (41.17±3.19) in diabetic patients as compared to control (165.5±35.5, 114.5±9.28, 94.4±34.4 and 48.17±3.4 respectively) ($p<0.001$) was noted. The atherogenic indices showed significantly increased levels of Atherogenic Index of Plasma (AIP) {(0.22±0.07) vs (0.04±0.01)} ($p<0.001$); Cardiac Risk Ratio (CRR) {(4.60±0.81) vs (2.44±0.71)} and Atherogenic Coefficient (AC) {(3.60±0.81) vs (2.44±0.71)} ($p<0.001$) in Type 2 diabetic patients vs control group.

Conclusion: All diabetic patients having at least one kind of dyslipidemia, assessment of atherogenic indices, especially atherogenic index of plasma gives valuable information about future risk of abnormal cardiac event. Thus, it could be a better marker and predictor for increased risk of CAD in Type 2 diabetes.

Keywords: Coronary artery disease, Diabetic dyslipidemia, Risk factor

INTRODUCTION

Diabetes mellitus is a group of metabolic disease triggered by total or partial insufficiency in insulin secretion or resistance to its function. This non-contagious disease is growing rapidly throughout the world [1]. In 2017, the incidence of diabetes was estimated to be 425 million individuals with age of 20 to 79 years and by the year 2045, the number will be anticipated to 629 million [2]. Developing Asian countries with a rapid industrialisation and contemporary lifestyle, faces the major issue of having the largest number of diabetic individuals, with prevalence of 69.2 million [3]. Diabetic patients have defective insulin secretion and decreased cell response. Chronic hyperglycemia of diabetes is associated with long-term damage, dyslipidemia and multiple organ failure predominantly including eyes, kidneys, heart and blood vessels. Diabetes and its associated complications reduce the quality of life and create massive social and economic burden [4]. Diabetic dyslipidemia involves, elevated triglyceride and Low Density Lipoprotein (LDL-C) whereas, reduced High Density Lipoprotein (HDL-C) are frequently noted. These lipid abnormalities may occur alone or in conjunction with other metabolic diseases [4,5]. Diabetic patients have 2 to 3 fold greater CAD risk, 4 fold greater risk of death from acute myocardial infarction, and 2 fold higher risk of post myocardial infarction morbidity as compared to non-diabetic [6].

Although some markers are available for cardiovascular risk assessment, they include Apo-lipoproteins, C-reactive protein, and marker of Insulin Resistance (IR). However, they are costly and are not regularly tested to evaluate the vulnerability of patients to cardiovascular disease. The term AIP suggested by Dobiasova M and Frohlich J, is comparatively newer indicator of plasma atherogenicity used to forecast risk of coronary heart disease [7]. The definition of AIP is a log of (TG/HDL-C) represents the equilibrium between protective and atherogenic lipoproteins [8]. Consequently, the plasma atherogenic index has lately been considered a powerful markers and a good predictor for the risk of atherogenicity and CAD.

The early assessment of atherogenic indices in addition to lipid profile provides an opportunity to reduce future risk of cardiac events in individual with uncontrolled diabetes. Therefore, the present study was undertaken with an aim to assess the cardiovascular risk in Type 2 diabetic patients using pattern of lipid profile; atherogenic indices including AIP, AC, and CRR and glycated haemoglobin levels.

MATERIALS AND METHODS

A case-control study was carried out from June 2017 to March 2019 in a tertiary care hospital. The study was approved by Institutional Ethics Committee {IEC registration number- MGMIHS/RS/2015-16}. Patients with history of chronic liver disease, kidney disease, malignancy, hypothyroidism and those with lipid lowering drugs were excluded from the study. After selection of appropriate study subjects, written informed consent was obtained from all participants. The sample size for Type 2 diabetes mellitus was calculated by considering the diabetes prevalence to be 9.3% in Mumbai [9]. According to this a minimal sample size of 130.54 was required and in the present study 280 subjects were included, of which n=70 were healthy age and sex matched controls recruited from volunteers who came for health check-up in the same hospital and 210 were diagnosed cases of Type 2 diabetes mellitus selected from Medicine and Diabetology OPD, with age group of 30-60 years. For controls 70 subjects which were convenient, (i.e., more than 30 subjects which were required for p-value calculation) was taken.

Diagnostic Criterion

- Diabetes was diagnosed; if the fasting plasma glucose ≥126 mg/dL or confirmed as per WHO criteria [10] or if there is a definite history of diabetes with records of treatment.
- Glucose tolerance was considered as normal if the fasting plasma glucose <100 mg/dL.
- Grading of severity of diabetes: Grade I severity: level of HbA1c is 6.5 to 8%, Grade II severity Level of HbA1c is 8.1 to 9% and Grade III severity level of HbA1c is >9%, [11].
- For the interpretation of serum lipid profile reference values were assessed based on the guidelines of National Cholesterol Education Programme (NCEP) and Adult Treatment Panel III (ATP-III) [12].
- According to NCEP-ATP III guidelines, hypercholesterolemia is defined as total cholesterol level >200 mg/dL, high LDL-C when value >100 mg/dL, hypertriglyceridemia as TG >150 mg/dL and low HDL-C when value is <40 mg/dL [12].
- Dyslipidemia was defined by the presence of one or more than one abnormal serum lipid concentration.

Anthropometric measurements: Height in centimetres, weight in kilograms, and Body Mass Index (BMI) was calculated as weight in kilograms divided by squared height in metres (weight in kg/height in m^2). For normal weight, BMI is 18.5 to 24.9 Kg/m^2, for overweight BMI is 25 to 29.9 Kg/m^2 and for obese 30 or more [13].

After 10 to 12 hours of fasting, 8 mL of blood sample was collected under aseptic condition by using BD vacutainers system. Of which 2 mL fasting (as well as post prandial that is after 2 hours of meal) blood were collected in a grey cap-sodium fluoride bulb for estimation of plasma glucose levels by glucose oxidase method, 2 mL of blood collected in purple colour cap Ethylene Diamine Tetra Acetic Acid (EDTA) bulb for measurement of glycated haemoglobin (HbA1c) on Nyco-Card reader and remaining 4 mL of whole blood collected in a red cap plain vacutainers. After 30 minutes of blood collection serum was separated for estimation of total cholesterol, triglyceride, and HDL-C by cholesterol oxidase peroxidase-end point method, glycerol phosphate oxidase-enzymatic method and Immuno-inhibitions method used respectively. All these routine biochemical parameters were processed on same day of sample collection on fully auto-analyser- Beckman Coulter Au480, (kits of Beckman Coulter, catalogue number: glucose-OSR6621, cholesterol- OSR6516, triglyceride- OSR 66118, and HDL-C- OSR6295). Whereas, LDL-C and VLDL-C were calculated by using Friedewald formula LDL= [TC-(TG/5)-HDL] and VLDL-C=TG/5 and also Non-HDL-C was calculated as Non-HDL-C= (Total cholesterol - HDL). Residual serum were stored at -70°C for 6 days and it was used to estimate fasting serum insulin level by sandwich Enzyme Linked Immunosorbent Assay (ELISA) method (kits from Chemux Bioscience) and read spectrophotometrically. Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR) calculated by formula HOMA-IR=fasting serum insulin (IU/mL)*fasting blood glucose (mmol/L)/22.5. The AIP was calculated as log of (TG/HDL-C), CRR was calculated as TC/HDL, and Ac was calculated by a using formula Ac=TC-HDL/HDL [14].

STATISTICAL ANALYSIS

Statistical analysis of data were done on SPSS version 20.0 software programmes for comparison of variables. Chi-square test and independent t-test and Pearson's correlation tests were used. Results were expressed as mean±standard deviation, and differences were considered to be significant at p-value <0.05 with 95% Confident Interval (CI).

RESULTS

The average duration of Type 2 diabetes was 9.8±4.4 years, majority of patients had diabetes between 6 to 14 years. In the present study diabetic patients average age was 53.5±6.7 years.

[Table/Fig-1] shows stratification of total diabetic subjects into three groups according to the age and majority of patients having age between 51-60 years, of which more were males (n=94) than females (n=42).

Age (years)	Sex	Male (%)	Female (%)	Total (%)
30-40	Controls	16 (33.33)	04 (18.18)	20 (7.13%)
	T2DM	19 (12.5)	08 (13.79)	27 (9.6%)
41-50	Controls	14 (29.16)	08 (36.36)	22 (7.9%)
	T2DM	39 (25.65)	08 (13.79)	47 (16.8%)
51-60	Controls	18 (37.5)	10 (45.45)	28 (10%)
	T2DM	94 (61.84)	42 (72.41)	136 (48.57%)
Total		200	80	280 (100%)

[Table/Fig-1]: Age and sex wise distribution of control and T2DM.

A significant difference of diabetic profile between control and Type 2 diabetes mellitus group is shown in [Table/Fig-2].

Parameters	Reference range	Controls	T2DM	p-value
BMI	18.5-24.9 (Kg/m^2)	21.97±2.18	26.0±4.25**	<0.001
BSL-F	70-110 mg/dL	91.8±6.39	169.0±44.4**	<0.001
BSL-PP	90-140 mg/dL	108.5±6.1	240.4±84**	<0.001
HbA1c	4.5-5%	4.9±0.32	8.8±1.5**	<0.001
Insulin	0.7-25 µU/mL	11.9±3.2	14.09±3.3**	<0.001
HOMA-IR	0.5-1.4	2.75±0.82	5.45±2.4**	<0.001

[Table/Fig-2]: Diabetic Profile in healthy Control and T2DM.
Differences between two groups were assessed by using Chi-Square test and independent t-test. BMI- Body mass index; BSL-F: Blood sugar level fasting; BSL-PP: blood sugar level post prandial; HbA1c: Glycosylated haemoglobin; HOMA-IR: Homeostasis model assessment for insulin resistance, **: Very significant

It can be observed that 56 patients had Grade I severity, 80 patients had Grade II severity and 74 patients had Grade III severity [Table/Fig-3].

HbA1c (%)	Male (%)	Female (%)	Total (%)
6.5-7.0%	11 (7.9)	05 (6.94)	16 (7.62)
7.1-8.0%	26 (18.84)	14 (19.4)	40 (19.04)
8.1-9.0%	48 (34.8)	32 (44.44)	80 (38.09)
>9.0%	53 (38.4)	21 (29.2)	74 (35.24)
Total (%)	138	72	210 (100)

[Table/Fig-3]: Distribution of diabetic patients according to the degree of glycemic control based on level of HbA1c [10].

The [Table/Fig-4] shows that all except LDL/TG were significantly higher among diabetic population. Diabetic patients are at high risk for the development of dyslipidemias.

Parameters	Reference ranges	Controls	T2DM	p-value
Total cholesterol	<200 (mg/dL)	165.5±35.5	188.3±31.9**	<0.001
Triglyceride	<150 (mg/dL)	114.5±9.28	161.33±19.4**	<0.001
HDL-C	>50 (mg/dL)	48.17±3.4	41.17±3.19**	<0.001
LDL-C	<130 (mg/dL)	94.4±34.4	114.9±30.9**	<0.001
VLDL	<30 (mg/dL)	22.9±1.85	32.26±3.8**	<0.001
LDL/TG	<0.67	0.82±0.29	0.71±0.20 NS	<0.491
LDL/HDL-C	<2	1.96±0.7	2.82±0.78**	<0.001
TG/HDL-C	<3	2.4±0.25	3.93±0.52**	<0.001
Non-HDL-C	<130 (mg/dL)	117.3±34.89	147.2±31.9**	<0.001

[Table/Fig-4]: Cardiovascular Disease Risk Factors of the Participants.
HDL-C: High density lipoprotein; LDL-C- Low density lipoprotein; VLDL-C- Very low density lipoprotein and TG: Triglyceride; Differences between two groups were assessed by using Chi-Square test and independent t-test; P**<0.001; P>0.05 NS; among cardiovascular risk factors we observed significantly high levels of lipid profile parameters with lipoprotein ratios (P**<0.001); except LDL/TG (P>0.05); **: Very significant

Significantly high levels in atherogenic indices in patients with Type 2 diabetes mellitus as compared to control were observed p<0.001 [Table/Fig-5].

Parameters	Reference ranges	Controls	T2DM	p-values
AIP	<0.11 (low risk) 0.11-0.21 (medium risk) >0.21 (high risk)	0.04±0.01	0.22±0.07**	<0.001
CRR	<4	2.44±0.71	4.6±0.81**	<0.001
AC	<3	2.44±0.71	3.6±0.81**	<0.001

[Table/Fig-5]: Atherogenic indices in Type 2 diabetes mellitus and control.
AIP: Atherogenic index of plasma; CRR: Cardiac risk ratio and AC: Atherogenic coefficient; differences between two groups were assessed by using Chi-Square test and independent t-test; **: Very significant

A significant positive correlation of atherogenic index of plasma (AIP) with the levels of Triglyceride (TG), Very Low Density Lipoproteins (VLDL-C) and the ratio of triglyceride to High Density Lipoprotein (HDL-C) (p<0.001**). Whereas, CRR and AC shows positive correlation with the serum levels of total cholesterol, LDL (P<0.001), and lipoprotein ratios including TG/HDL (P: 0.021), LDL/HDL and LDL/TG (P<0.001) in diabetic patients [Table/Fig-6].

Parameters	r-value	p-value
AIP with		
Triglyceride (TG)	0.837	<0.001**
VLDL-C	0.837	<0.001**
TG/HDL	0.996	<0.001**
CRR and Ac with		
Cholesterol	0.898	<0.001**
LDL-C	0.937	<0.001**
TG/HDL-C	0.364	0.021*
LDL/HDL	0.992	<0.001**
LDL/TG	0.815	<0.001**

[Table/Fig-6]: Correlation of atherosclerotic indices with other cardiovascular risk factors in T2DM.
Pearson's correlation tests were used; *: Significant; **: Very significant

DISCUSSION

Diabetic subjects are overweight (BMI 26.09±4.2 kg/m^2) with poor glycaemic control (HbA1c is 8.8±1.5%). HbA1c is done to monitor the diabetic control over the period of last three months and it is significantly correlated with the level of triglyceride (r=0.314, p<0.05). Thus, level of glycemic control is the indirect indicator of dyslipidaemia in Type 2 diabetes. Among insulin resistance, it was found that there was high level of HOMA-IR in diabetic subjects 5.45±2.4 as compared to control. Thus, overweight, obesity and physical inactivity are the key risk factors for various chronic conditions, including hypertension, dyslipidemia and diabetes, these findings are in agreements with Du G et al., [15].

In the present study, it was observed that more than 87% of diabetic subjects have at least one kind of dyslipidemia especially high levels of triglyceride, LDL-C and low-level of HDL-C as compared to control. In diabetic patients, BMI shows positive correlation with LDL-C (r= 0.304, p<0.05) which were in accordance with Akholkar PJ and Gandhi AA [16].

The present study findings are in accordance with Mahfuza A et al., they found that high level of TC, TG and LDL-C 47.3%, 76.7% and 41.3% respectively; and 60% low levels of HDL-C in diabetic patients. They also observed that positive correlation of fasting blood glucose with TC (r=0.169, p=0.003), TG (r=0.421, p≤0.001), LDL-C (r=0.077, p=0.185), while negative correlation with HDL (r=-0.049, p=0.397) [17]. The prime index of CVD evaluation is LDL-C, but LDL-C alone does not provide adequate information about atherogenic risk in patients with hypertriglyceridemia [18].

Atherogenic indices; including AIP, CRR and AC were observed to be significantly increased in subjects with T2DM as compared to control, these finding are in agreement with Mahfuza A et al., and Adu EM et al., [17,18]. In the present study, the observations are increased level of CRR in T2DM (4.59±0.81) as compared to control (2.44±0.71). This is in accordance with work done by Adu EM et al., their findings are significantly high CRR values 4.1±3.0 in diabetic individual when compared with control 1.9±3.0. [18]. When comparing the value of CRR in diabetes and control with the value of American Heart Association is ≤3.5, the diabetes shows higher tendency to CVD [19].

AC in diabetes was observed to be significantly high when compared with the non-diabetic healthy controls. This is in agreement with Bhowmik B et al., their findings of Ac levels in diabetes are significantly higher 3.1±2.0 than control 0.9±2.0 [19]. Therefore, early screening of lipid disorders are highly recommended for the primary and secondary care prevention of T2DM and related risk or complications. AIP is a mathematical relationship between log of TG and HDL-C, an additional index for cardiovascular risk assessment. AIP values of -0.3 to 0.1 were suggested to be associated with low cardiovascular risk, 0.1 to 0.24 is medium risk and >0.24 associated with higher cardio vascular risk. This ratio has a powerful predictor of Myocardial Infarction (MI) and quantifies the response to therapeutic intervention [20]. Among all lipoprotein markers, AIP was positively associated with Gensini score [21]. The present authors found significantly high levels of AIP in diabetic subjects as compared to control; an increase in AIP indicates a decrease in the diameter of LDL particle and increase in the proportion of sdLDL that are more prone to oxidation, which also promotes the formation of foam cells. LDL-C with oxidised apo-protein B is regarded as highly atherogenic characteristic.

LIMITATION

Follow-up monitoring from the first day of disease diagnosed to the disease progression is required for at least 5 years, which is one of the limitations of the present study.

CONCLUSION

Lipoprotein ratios and atherogenic indices particularly AIP are not routinely involved in lipid profile. They are the better markers in the assessment of cardiac risk in patients that are more prone to develop coronary artery disease such as uncontrolled diabetes mellitus with dyslipidemia. These indices are the good predictor and indicator for follow-up monitoring in patients with high risk Type 2 diabetes mellitus. Thus the present authors recommend the inclusion of these atherogenic indices in routine lipid profile panel.

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