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"COMPARISON OF ATHEROGENIC INDEX OF PLASMA AND CHOLESTEROL/HDL RATIO AMONG TYPE 2 DIABETES MELLITUS PATIENTS IN A TERTIARY CARE HOSPITAL"

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ABSTRACT Lipid profile though is a well established parameter to predict cardio vascular risk in patients suffering from type 2 diabetes mellitus(T2DM), at present lipid ratios are replacing these age old parameters. Among the lipid ratios Atherogenic index of plasma(AIP) and cholesterol/HDL(Chol/HDL) are found to be of great significance. This cross-sectional study aimed to compare the predictive value of two lipid ratios, "Atherogenic index of plasma" (AIP) and "Cholesterol/HDL ratio" on basis of insulin resistance (IR) among 55 newly diagnosed cases with Type 2 Diabetes Mellitus (T2DM) and 50 control subjects. HOMA –IR (p value <0.0001), AIP (<0.001) and Cholesterol/HDL ratio (<0.001) were significantly raised among case group in comparison to controls. Both AIP(r- 0.305, p-0.002) and Chol/HDL ratio(r- 0.23, p value- 0.018) was significantly correlated with HOMA-IR. ROC curve of AIP and Chol/HDL ratio was plotted for identifying IR. There is no significant difference between areas under curve (AUC) of AIP (AUC-0.656) and Chol/HDL ratio(AUC-0.630) (p value- 0.49). AIP was found to be correlated better with Insulin resistance than CHOL/HDL ratio. AUC in AIP was found to be slightly higher and overall sensitivity and specificity of AIP was found to be 66% and 69%, of Chol/HDL ratio was 46% and 76% to identify moderate to high-risk group: whereas it is 69%&47% of AIP and 87% and 32% of Chol/HDL ratio to identify low risk group. Both lipid ratios have some significance in predicting cardio vascular risk in T2DM

KEYWORDS : AIP, Chol/HDL ratio, insulin resistance

INTRODUCTION

The rise of Diabetes Mellitus (DM) in 21st century is one of the major public health problems. The total diabetic population in India (20-79 years) was 77 million on 2019 with prevalence >10% and expected to rise to 115million by 2030 in south East Asia region. Under physiological condition: insulin stimulates the entry of glucose in tissues like heart: skeletal muscle: liver and adipose tissue. In cases with Type 2 Diabetes mellitus (T2DM): as a result of Insulin resistance: this process is hampered.[1] Then pancreas attempts to compensate the deficiency by increasing secretion of insulin resulting in hyperinsulinaemia. A strong correlation between Insulin Resistance (IR) and risk to develop cardiovascular disease (CVD) has been established [2]. Underlying mechanisms include atherosclerosis development: hypertension and macrophage accumulation [3]. The patients with T2DM have been reported to increased risk of developing CVD: which is one of the macrovascular complications and primary cause of death in diabetic patients. The underlying pathology of macrovascular complications starts with atherosclerotic plaque formation. Though there are multiple risk factors of developing atherosclerosis and CVD: T2DM acts as an independent risk factor for the development of ischaemic disease and death. This increased risk justifies the identification of dyslipidaemia in T2DM patients. Numerous studies have shown decreased risk of macrovascular disease in patients with T2DM: who had been treated with lipid lowering agents [4]. The lipid ratios have replaced the isolated lipid parameters of lipid profile as risk predictor for CVD. One such lipid ratio is cholesterol HDL Ratio. Recently another parameter: known as Atherogenic index in plasma (AIP) has emerged as predictive marker for atherosclerosis and CVD [5]. Many studies have found association between insulin resistance and AIP. But no study has been so far found to compare these 2 indicators (Cholesterol HDL Ratio and AIP) in patients with T2DM.

This study was undertaken to compare these 2 indicators on basis of Insulin Resistance and as risk predictor of CVD in patients with T2DM.

MATERIALS AND METHODS

This cross-sectional study was performed in the Dept. of Biochemistry of NRS Medical College: Kolkata in 2019. Newly diagnosed diabetic patients in the age group of 18-60 years were selected as cases. Diagnosis of Diabetes Mellitus was established using American Diabetes Association criteria[6]. Presence of chronic kidney disease: liver disease: type 1 DM: Pregnancy: Patients who are taking insulin: oral hypoglycemic drugs or lipid lowering drugs were excluded from study.Healthy persons were treated as control. This study was approved by institutional ethics committee. A preformed questionnaire and consent form had been prepared and was used for relevant history: medication.

Approximately 7 ml Blood was collected at fasting state with a standard aseptic procedure after obtaining informed consent: (1 ml in glucose vial 3 ml in EDTA vial: and 3 ml in vial without anticoagulants). Blood was centrifuged to separate plasma from EDTA vial and serum from vial without anticoagulants. Fasting Plasma glucose(FPG): was estimated from fluoride vial: EDTA vial was used to estimate HbA1c: lipid profile and Insulin from clotted vial.

FPG: lipid profile was estimated by fully automated Biochemistry analyzer. HbA1C was estimated using Hb-Vario kit (HPLC) on the Hb-VarioAnalyser. Insulin level was determined by ELISA method using commercially available kit. The HOMA2 model is used to yield an estimate of insulin resistance: insulin sensitivity and β-cell function from fasting plasma insulin and glucose concentrations using HOMA 2 [7] calculator(from www.OCDEM.ox.ac.uk). The cut off value for defining HOMA2-IR is more than 1.8 [8]. AIP was calculated according to the formula: log(TG/HDL-C). An AIP value of under 0.11 is considered as low risk of CVD; the values between 0.11 to 0.21 and upper than 0.21 are considered as intermediate and increased risks: respectively [5]. Cholesterol/HDL ratio was calculated by Total cholesterol/HDL value. Descriptive Analysiswas made by using SPSS software. Receiver operating characteristic (ROC) curve analysis was performed for AIP and for cholesterol/HDL ratio: to discriminate those subjects who were insulin resistant from those who were insulin sensitive. This was done by the method proposed by DeLong et al using Medcalc software

RESULT ANALYSIS

In this case control study: a total of 105 subjects were recruited comprising 55newly diagnosed cases and 50 controls. Among 55newly diagnosed cases: 20 were male and 35 were female: whereas the male female ratio is 27:23 among controls.

T2DM cases were confirmed by estimating Fasting blood glucose (FPG) and HBA1C. Table 1 shows values of HOMA IR: Cholesterol HDL ratio and AIP: calculated with help of appropriate formula and expressed as Mean $\pm$ SD.The comparison for significance of study parameters among 2 groups was done by student t test. P value < 0.05 is considered as significant.AIP when calculated from these 2 parameters was found to be significantly altered in our study. It was found to be 0.30 ± 0.2 in cases in comparison to 0.08 ± 0.20 in control group.

Table 1: Biochemical Parameters in study population

Parameter	Control (n =50)	Cases (n =55)	Control vs Cases* T value (p value)
Insulin(μIU/mL)	10.65± 2.35	13.97± 6.16	3.58(0.0005)
HOMA IR	1.41±0.30	2.09±0.91	5.089(<0.0001)
Cholesterol(mg/dl)	165.8± 38.1	198.78± 49.13	3.8(<0.001)
HDL(mg/dl)	45.84± 9.30	41.49± 8.03	2.57(0.0116)
TG(mg/dl)	131.6± 53.23	205.30± 97.70	4.7323(<0.0001)
AIP	.0798± 0.19	0.298± 0.2	5.5 (<0.001)
Chol/ HDL ratio	3.73± 1.02	4.85±1.12	5.3 (<0.001)

All values are expressed in Mean ± SD: *Significance tested by Student t test

Cholesterol/HDL ratio was found to be 4.8±1.1 in cases in comparison to 3.7±1.02 in control group. Correlation of 2 lipid ratios with Insulin Resistance was calculated by Pearson's correlation coefficient. Both parameters are significantly correlated with insulin resistance (Table 2).

Table 2: Correlation of 2 lipid ratios with Insulin Resistance

Correlation between	Correlation coefficient (r value)	p value
AIP vs IR	0.305	0.002
Chol/HDL ratio vs IR	0.23	0.018

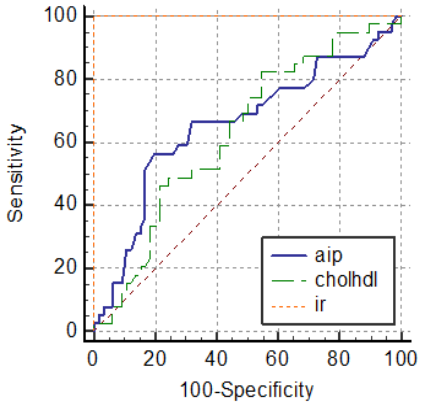
Table 3 shows Comparison of 2 lipid ratios as risk predictor of CVD.

Table 3: Comparison of 2 lipid ratios as risk predictor of CVD

Biochemical parameter	Area under curve (AUC)	Cut off value for risk calculation	sensitivity	specificity
AIP	0.656	<0.11 (Low risk)	69%	47%
		>0.22 (Moderate to High risk)	66%	69%
Chol/HDL	0.630	<3.5 (Low risk)	87%	32%
		>5.0 (Moderate to High risk)	46%	76%

ROC analysis of AIP and Chol/HDL ratio for identifying IR is presented in Fig 1. There is no significant difference between areas under curve (AUC) of AIP and Chol/HDL ratio (p value- 0.49).

Fig 1: ROC analysis of AIP and Chol/HDL ratio



AUC of AIP- 0.656, SE- 0.06; AUC of Chol/HDL ratio- 0.630, SE -0.05

DISCUSSION

The pathogenesis of type 2 diabetes is complex and: in most instances: clearly requires defects in both β-cell function and insulin sensitivity[1]. Hyperinsulinemia is the classic indicator of insulin resistance and may itself contribute to the insulin resistance in T2DM. In this study insulin level was found to be 13.97(μIU/mL)±6.16 whereas HOMA IR in the newly diagnosed cases are found to have more insulin resistance (2.09±0.91) in comparison to non-diabetic healthy individual (1.41±0.30). The change in insulin level was in accordance to the result obtained by Edavan P. Praveen et al [9]. According to Bruno Gelonze et al: cut off values for insulin resistance was >1.8 [8].

Dyslipidemia is a well-known consequence of T2DM. In this study: the concentration of Cholesterol and Triglyceride have been found to be significantly high whereas HDL level was found to be significantly low in diabetic cases in comparison to normal (Table 1). Compensatory hyperinsulinemia due to Insulin Resistance induces increased free fatty acid (FFA) efflux from adipose tissue: thus raising VLDL production in the liver and: consequently: plasma triacylglycerol is increased[10]. Reducing HDL-C can be explained by activation of cholesterol ester transfer protein (CETP) and increased clearance by the kidneys**.**Reduced cholesterol absorption and increased cholesterol synthesis have been demonstrated in patients with type 2 diabetes: which has been suggested due to increased expression of *SREBP[11]* encoding sterol regulatory element-binding protein: a factor regulating cholesterol uptake and synthesis: observed in T2DM.

In peripheral tissues: in normal conditions insulin initiates its action by binding to insulin receptor. This induces conformational changes of the insulin receptor: which in turn causes receptor dimerization and activation of the tyrosine kinase domain of the intracellular part of the β-subunit activating a cascade of phosphorylation events. This can produce two classes of effects. The common one is "metabolic" effect that promotes glucose utilization and preservation of glycogen and lipid. But when there is hyperinsulinemia due to insulin resistance: the pathways leading to metabolic effects of insulin get hampered. As a result: the second class of effect is promoted which is a growth- and differentiation-promoting effect. This pathway leads to promotion of inflammation and atherogenesis and is mediated by the activation of Ras (mostly through shc and: to a lesser degree: IRS proteins): Raf: and mitogen-activated protein kinases (MAPK) ("growth signaling pathway")[12]. This atherogenesis is the basis of macrovascular complications and death in patients with T2DM[1]. So: Early assessment and control of CVD risk factors in patients with T2DM has a positive effect on reducing the risk of CVD and death in patients and improving the prognosis of patients.

For long time Total cholesterol /high-density lipoprotein (HDL) cholesterol ratio was considered as risk indicators of atherosclerosis with greater predictive value than isolated lipid parameters used independently. Cholesterol/HDL ratio has been considered as a predictor of atherosclerosis [13].

AIP: emerged as predictive marker for plasma atherogenecity[14]: was described by Dobiasova and Frohlich[15] . A previous study showed that the value of AIP was inversely associated with diameter of LDL particle[16].

In this study level of AIP was found to be significantly ($p<0.001$) increased among (0.298± 0.2) case group in comparison to control(0.07±0.19) and Chol/HDL ratio also raised ($p<0.001$) among case group(4.8±1.1)than control group(3.7±1.02) (Table 1)

As Insulin resistance is basic cause behind the dyslipidemia correlation of these 2 ratios with Insulin Resistance was calculated. AIP was found to be correlated better with Insulin resistance (AIP vs IR- r- 0.305; p-0.002 , Chol/HDL ratio vs IR –r- 0.23; p-0.018)(Table2). Zhen Li et al in 2018 demonstrated similar finding that AIP was correlated with HOMA IR[17].

So far ROC analysis was performed: AUC(0.656) in AIP was found to be slightly higher. In 2017 Halef Okan Doğan showed similar findings [18]. Overall sensitivity and specificity of the parameter was found to be 66% and 69% to identify moderate to high-risk group: whereas it is 69%&47% to identify low risk group. So far chol/HDL ratio is concerned: sensitivity and specificity of the ratio to identify low risk group is 87% and 32% and 46% and 76% to identify high risk group cases (Table 3 & Fig 1).

CONCLUSION

Routinely all the parameters of lipid profile are estimated in type 2 DM patients. So we can calculate both the ratios, AIP and Chol/HDL ratio to have a better understanding of development of cardiac risk as the sensitivity of AIP is better in moderate to high risk group and specificity in low risk group respectively. But specificity of Chol/ HDL ratio is higher in high risk group and sensitivity in low risk group.

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ABBREVIATION:

Type 2 diabetes mellitus- T2DM

Atherogenic index of plasma- AIP
Cholesterol/HDL- Chol/HDL
Insulin resistance- IR
Areas under curve- AUC
Cardiovascular disease – CVD

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