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ESTIMATING CORRELATION OF HbA1c WITH ATHEROGENIC INDEX OF PLASMA AND ATHEROGENIC COEFFICIENT IN TYPE 2 DIABETIC PATIENTS FOR ASSESSING CARDIOVASCULAR DISEASE RISK

Clinical Biochemistry

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ABSTRACT

Increasing prevalence made type 2 diabetes mellitus (T2DM) a global health problem. Increased HbA1c, Atherogenic Index of Plasma (AIP) and Atherogenic Coefficient (AC) are risk factors and predictable markers of CVD risk. Venous blood sample of 120 subjects were collected. Their Fasting and postprandial blood sugar (FBS & PPBS),HbA1c, Triglyceride (TG), Total Cholesterol (TC) and HDL cholesterol were tested by enzymatic analysis kits. AIP was calculated by using formula Log10 (triglyceride/HDL-c) and AC was calculated as ratio of (TC-HDL-c/HDL-c).Association between all variables was obtained by Pearson's correlation test and student t test was used to compare cases and controls groups. Our study shows HbA1c, AIP and AC are significantly higher in diabetic patients than healthy controls. Present study suggests HbA1c, AIP and AC can be utilized for screening patients with high risk of diabetic complications.

KEYWORDS

AIP, AC, T2DM, CVD.

INTRODUCTION:

T2DM is a chronic metabolic disorder where hyperglycemia occurs due to reduced insulin secretion from β-cells of pancreas or insulin resistance hampering its functional ability and in long run, organs like eyes, kidney, nerve, heart and blood vessels get damaged. Rapidly increasing prevalence of diabetes raised issues like individual suffering and increased healthcare bills thus T2DM has became global public health problem[1,2,3,4,5]. Out of total diabetes cases, almost 90% are of T2DM[1].540 million people are affected worldwide and India is the second most affected country and till 2030 diabetic population may reach 80 million in India alone[3,6]. Chronic complication development risk increases with duration of disease including micro-vascular complications like neuropathy, nephropathy, retinopathy and macro-vascular complications that include CVD, stroke,peripheral artery disease[3]. CVD has high morbidity and mortality and almost 70% deaths of diabetic patients are due to CVD[3,6,7]. CVD shows early onset and great severity in diabetic patients and its other risk factors like hypertension and dyslipidemia are commonly associated with T2DM.DM is preventable and reversible condition if diagnosed early andtreated timely preventing CVD risk and death in diabetic patients[5,7,8].

Glycated haemoglobin i.e. HbA1c estimates the amount of glucose binds with haemoglobin present in RBC which provides long-term glycemic control of 2-3 months which is equivalent to the life span of RBC. Thus HbA1c is now a day used as a gold standard of glycemic control and marker of CVD risk. According to American Diabetes Association, 1% rise in HbA1c increases CVD risk by 18%, mortality by 25% and micro-vascular complications by 35% and 0.2% reduction of HbA1c reduces mortality rate by 10%[2,3,6,9].

Dyslipidemia is the major risk factor of coronary artery disease and other cardiovascular events as it is a major atherogenic factor[6,9]. According to Adult Treatment Panel III, HDL &TG combination contributes to atherogenic dyslipidemia[6,10]. Hypertriglyceridemia and low HDL-c are independent markers of CVD risk and AIP combines them into a single biomarker improving its diagnostic capacity making it a novel biomarker, thus exhibit greater sensitivity for CVD risk as compared to individual lipid parameters[11,12]. AC measures cholesterol in LDL,VLDL & IDL with respect to HDL-c[10]. Both AIP & AC are simple and easy to calculate parameters and due to their affordable and accessible nature these biomarkers can be used as predictor and follow-up monitor of CVD risk in clinical practice[5,7,8].

This study is done to find correlation of HbA1c with AIP & AC assess CVD risk in T2DM patients as these parameters can be easily calculated from routinely done lipid profile in small settings where comprehensive laboratory testing is inconvenient.

MATERIALS & METHODS:

Total 120 subjects, aged between 30-60years coming to Department of Biochemistry, GMC Aurangabad were studied after taking informed consent from patients &ethical approval from Institutional Ethical Committee. 60 cases diagnosed with T2DM were included in study & 60 age and sex matched healthy subjects were taken as control. Exclusion criteria include history of smoking, alcoholism, malignancy or thyroid disorder.

Venous blood samples from all subjects were collected after overnight fasting. Parameters were analyzed by kit based enzymatic methods. Fasting and postprandial blood sugar (FBS & PPBS) analyzed by GOD-POD method, triglyceride(TG) by lipase/Glycerokinase/ Glyceophosphate oxidase method, total cholesterol(TC)&HDL-c by Cholesterol-oxidase peroxidase method &HbA1c by turbidometric method. AIP was calculated through online calculator of atherogenic risk based on formula log 10 (TG/HDL-c) similarly AC is also calculated on online calculator based on the formula i.e. (TG-HDL-c/HDL-c).

All biochemical parameters in cases and control groups were compared by student t test and association between all parameters are obtained through pearson's correlation analysis. Data were analysed using SPSS software version 16.

RESULTS:

60 T2DM cases and 60 healthy controls aged between 30-60 years with equal number of males and females were studied. According to WHO criteria, Fasting blood glucose ≥126mg/dl and postprandial blood glucose ≥200mg/dl confirms diagnosis of T2DM.

Table 1: Comparison Of Biochemical Parameters In Cases And Controls

Parameters	CASES (n=60) Mean ± SD	CONTROL (n=60) Mean ± SD	p value
Age	51.4 ± 7.28	45.5 ± 9.18	<0.001

HbA1C	8.45 ± 1.52	5.13 ± 0.50	<0.001
FBS	169.85 ± 80.30	85.66 ± 12.46	<0.001
PPBS	253.55 ± 99.81	114.73 ± 16.52	<0.001
TC	209.51 ± 52.29	158.06 ± 21.02	<0.001
TG	218.8 ± 100.94	104.2 ± 37.38	<0.001
HDL	39.45 ± 7.71	46.38 ± 6.47	<0.001
AIP	0.35 ± 0.19	-0.02 ± 0.16	<0.001
AC	4.53 ± 1.87	2.45 ± 0.60	<0.001

P value <0.001 is highly significant

Table no. 1 shows comparison between biochemical parameters in cases and controls groups showing all parameters except HDL-c were significantly higher in cases compared to control group. T2DM patients in cases had poor glycemic control and showed dyslipidemia which leads to increased CVD risk.

Table 2: Correlation Of HbA1c With AIP AND AC And Other Parameters

parameters	r value	P value
FBS	r = 0.767	<0.001
PPBS	r = 0.874	<0.001
TC	r = 0.490	<0.001
TG	r = 0.585	<0.001
HDL	r = -0.350	<0.001
AIP	r = 0.678	<0.001
AC	r = 0.495	<0.001

P value <0.001 is highly significant

Table no. 2 shows highly significant positive correlation between HbA1c and FBS, PPBS, TC, TG, AIP and AC except HDL-c which shows negative correlation with HbA1c.

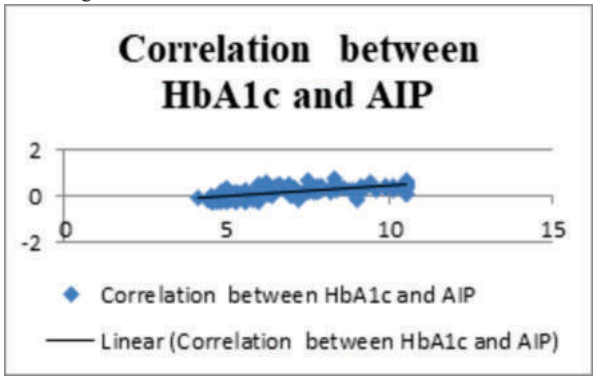

Chart 1: Correlation between HbA1c and AIP was r = 0.678with p value < 0.001

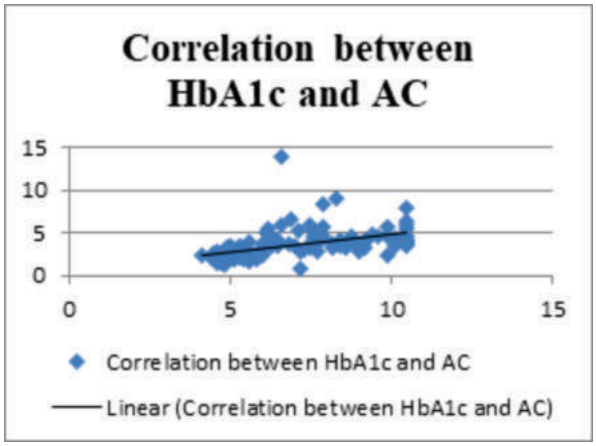

Chart 2: Correlation between HbA1c and AC was r = 0.495 with p value < 0.001

Our study cases with T2DM had poor glycemic control so more prone to CVD risk and high value of AIP in cases indicate it can act as marker to identify CVD risk.

DISCUSSION:

Almost 1.5 million deaths due to diabetes had occurred in year 2019. In diabetic patients, more severe CVD develops at an early age so to find diagnostic marker which can detect the disease early is important[8]. 65.8% T2DM patients predicted to be on high risk of CVD within 10years[13].T2DM is a chronic hyperglycaemic condition where onset of Insulin deficiency is either due to reduced secretion from pancreatic β-cells or insulin resistance due to inability of β-cells to cope up with raised demand of insulin developing reduced glucose uptake by tissues which increase insulin production further decreasing insulin sensitivity by tissues[5,14].

As vascular complications are more prevalent in T2DM, in long run vascular endothelium gets damaged so decreasing functional lipoprotein lipase causing high TG & low HDL-c thus accelerating atherosclerosis, retinal microvasculature damage causing retinopathy and visual impairment & damage to kidney causing kidney failure. So, identification of risk factors is essential here[4,9,10]. T2DM is an established risk factor for CVD and increases its risk by 2-4 folds. CVD include Myocardial infarction, unstable angina, stroke and heart failure etc. CVD risk increase with duration of disease and associated comorbidities.[13].

According to Diabetic complication & management Trail, HbA1c is a gold standard for providing long term glycemic control of almost 6-8weeks[1,3]. It is user friendly & more stable test as can be done anytime without fasting showing minimum biological variability[6]. Raised HbA1c level shows poor glycemic control & increased severity of dyslipidemia[2]. As glycemic control affects serum lipid levels, together both are predominant risk factors & can be used to screen diabetic patients at high risk[3,6].

Normal healthy person with good lipid profile presents LDL<100mg/dL, HDL>50mg/dL and TG<150mg/dL and abnormal alterations in it is known as dyslipidemia[1]. T2DM presents with hypercholesterolemia, hypertriglyceridemia, increased Apolipoprotein-B, free fatty acid & Small dense Low Density Lipoprotein cholesterol (sdLDL-c) and reduced HDL-c mainly due to insulin resistance collectively known as diabetic dyslipidemia and all these combined or alone increases CVD risk[4,13,14].

Atherogenicdyslipidemia further deteriorates insulin resistance especially TG being the most abundant lipid in adipose tissue so its increased level cause biotoxicity further worsening insulin resistance and glycemic control through stress &inflammation by lipotoxic effect & cytokines released. Insulin resistance fat cells release excess free fatty acids stimulating TG formation that will raise Apo-B & VLDL levels. Thus, glycemic and lipid control are inter-related and affect each other[3,5,14].

There are 3 different forms of LDL i.e. small dense, particle & oxidized[13]. Predominant LDL form is sdLDL that easily penetrate vascular endothelium and bind to glycoprotein present at arterial wall where it gradually deposits, sdLDL also oxidized easily then phagocytised by macrophages&tansforms to foam cells that induce atherosclerotic plaque formation developing atherosclerosis. sdLDL decreases antioxidant production further accelerating atherosclerosis[3,14,15,16]. Due to complex technique & high cost, sdLDL regularly not done in clinical practice so can be assessed by AIP indirectly[13,16].

Atherogenic Coefficient represented as (TC-HDL-c)/HDL-c so prediction of CVD risk through ACrelies on HDL-c. It can also be represented as Non-HDL-c/HDL-cwhereNon-HDL-c is TC-(LDL+VLDL+IDL) so AC measures cholesterol in all these fractions with respect to HDL-c reflecting atherogenicity by whole spectrum of lipoprotein fractions[10]. Thus by comparing atherogenic and protective lipoproteins for their cholesterol content, broad spectrum of atherogenic assessment is obtained through AC than LDL[14]. Non-HDL-c is analogue to Apo-B in lipoprotein burden assessment and as its assay is unavailable and unaffordable, AC can replace it due to its simple calculation and easy availability of lipid profile where comprehensive laboratory tests not available[10].

AIP is molar concentration of TG & HDL-c in its logarithmically transformed ratio showing association between protective & atherogenic lipoproteins. It can predict LDL particle size & inversely correlate with it. AIP is independent of LDL so is a more promising atherogenic predictor than LDL[8,13,14,16]. AIP has 3 ranges depending on

the level of CVD risk i.e. <0.11= low risk, 0.11-0.21= intermediate risk &>0.21= high risk[8]. Even if other lipid parameters came out to be normal, AIP can assess hidden risk& can be obtained by simple formula from lipid profile making it a good predictor of CVD risk[2,3]. AIP can assess atherosclerosis, CVD, insulin resistance& metabolic syndrome. AIP in T2DM patients mainly predict coronary artery disease (CAD) which is the most common CVD risk[4,13].AIP act as low-cost surrogate marker reflecting both TG/HDL-c ratio & LDL-c particle size and is surrogate for insulin resistance as it is equally reliable as fasting serum insulin. Insulin resistance associates with high TG &low HDL so AIP is also called as dual biomarker as it predicts abnormal lipid &glycemic metabolism simultaneously[6,8,12].

High level of AIP shows severe form of CVD risk with worse prognosis leading to poor outcome &is associated with high incident of stroke & myocardial infarction[16]. AIP can be easily derived from regular lipid profile without any additional cost making screening of high risk diabetic patients cheap & easily available[13].AIP can be improved by dietary modification and exercise[7]. When TG & HDL-c levels are managed, AIP level naturally reduced[16].As glycemic and lipid control are inter-related and detected by AIP so diabetic patients can be treated with hypoglycaemic drugs with lipid lowering drugs which reduce AIP[9]. Thus, AIP can be used for follow-up monitoring of T2DM patients with high risk[7].Monitoring AIP continuously lowers incidence & decrease burden of CVD in society[12].

AIP & AC monitors atherogenicity thus called as atherogenic markers as can predict atherosclerosis and CVD risk[14]. Our study evaluates correlation of HbA1c with AIP & AC for screening of diabetic patients to predict CVD risk &its early intervention to prevent adverse effects. Other studies, indicates similarity to our study showing high AIP & AC in T2DM patients to predict CVD risk and strong positive correlation between HbA1c, AIP & AC. Lumu W et al done study in T2DM patients of Uganda showed findings contrast to our study and did not present significant correlation of AIP with FBS and HbA1c without unclear reasoning even though mean HbA1c strongly related to CVD. Causal relation can't be established due to study being cross sectional.

CONCLUSION:

Poor glycemic control patients possess atherogenic lipid profile and HbA1c not only monitor glycemic control but can also provide information of dyslipidemia. Poor glycemic control and dyslipidemia are inter-related so affecting each other and can screen diabetic patients with high risk and predict CVD risk. AIP and AC can be easily calculated from routine lipid profile so their regular monitoring can take care of glycemic control and dyslipidemia simultaneously. Small sample size and inability to follow-up due to limitedtime and resources are the limitation of our study. This study proves there is a strong association of HbA1c with AIP & AC and these parameters can act as biomarkers of CVD risk in T2DM patients.

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