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ATHEROGENIC INDEX OF PLASMA, CASTELLI RISK INDEX AND ATHEROGENIC COEFFICIENT- NEW PARAMETERS IN ASSESSING CARDIOVASCULAR RISK

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ABSTRACT

Coronary artery disease is the epidemic of modern civilization in which dyslipidemia contributes significantly to its pathogenesis. We studied the significance of three important lipid ratios i.e. Atherogenic Index of Plasma (AIP) {(logTG)/HDLc}, Castelli's Risk Index I & II (TC/HDLc and LDLc/HDLc respectively) and Atherogenic coefficient (AC) {(Non-HDLc)/HDLc} in predicting the risk of CAD. A case-control study was conducted with 60 angiographically confirmed patients and 60 healthy volunteers. Lipid profile {Total cholesterol (TC), Triacylglycerol (TG), HDLc, LDLc} was measured on automated analyser and ratios were calculated for both case and control groups. Statistical analysis was done using SPSS software. TC and LDLc were not different between the two groups. But the ratios based on these parameters were significantly different ($p<0.05$). These ratios can contribute significantly to the estimation of risk of CAD especially when absolute values of lipid profile parameters are not markedly deranged or in centres with insufficient resources.

KEY WORDS

Atherogenic Index of Plasma, Castelli's Risk Index, Atherogenic coefficient, Coronary artery disease, Dyslipidemia, Lipid ratios

INTRODUCTION

WHO predicts 11.1 million deaths globally and 71% deaths in developing countries due to Coronary Artery Disease (CAD) by 2020 A.D. [www.who.int/ncd/cvd]. Over the last few decades, several risk factors have been found to be associated with CAD like smoking, age, sex, diabetes, hypertension etc. Despite lower prevalence of such risk factors in Asians, incidence of CAD has been reported to be high and is constantly rising [1]. Changing life style patterns in Indians are reflected by rising incidence of abdominal obesity, impaired glucose and other metabolic changes. Dyslipidemia has been identified as one of the most important risk factor associated with CAD by the INTERHEART- South Asia study [2]. Low HDLc, high TG and high LDLc levels have been associated with increased incidence of CAD [3,4].

Despite such studies, in the absence of an abnormal lipid profile the possibility of CAD cannot be ruled out. It has been suggested that the different combinations of these lipid profile parameters can be used to identify such high risk individuals. Atherogenic Index of Plasma (AIP), Castelli Risk Index (CRI) and Atherogenic Coefficient (AC) are the three ratios we studied in predicting the risk of CAD. These are the calculated fractions which can be used in the clinical

setting for assessing the risk of cardiovascular disease beyond the routinely done lipid profile.

Atherogenic Index of Plasma (AIP) is based on two important parameters TG and HDLc, both of which are independent risk factors for CAD [5]. Castelli Risk Index (CRI-I) calculated as (TC/HDLc) and (CRI-II) as (LDLc/HDLc) is another fraction which involves independent risk factors for CAD[6,7]. Atherogenic Coefficient (AC) calculated as {(TC- HDLc)/HDLc} is yet another ratio relying on the significance of HDLc in predicting the risk of CAD [8].

Thus, the present study was conducted with the objective of assessing the significance of lipid ratios like Atherogenic Index of Plasma (AIP), Castelli Risk Index (CRI) and Atherogenic Coefficient (AC) in identification of at-risk individuals for CAD beyond the routinely done lipid profile especially in insufficient resource situations.

MATERIALS AND METHODS

The study was conducted jointly by the Department of Biochemistry, Department of Medicine and Cardiology of the tertiary care hospital. The institutional ethics committee had approved our study. As many as 120 subjects were enrolled in our study after informed written consent. The study subjects were divided into two groups. Case group had 60 angiographically confirmed patients of coronary artery disease in the age range of 35-60 years attending cardiology OPD of Lady Hardinge Medical College and associated hospitals and GB Pant hospitals, New Delhi, India. Control group consisted of 60 age and sex matched apparently healthy volunteers.

All subjects were non-smokers, non-alcoholics, and there was no positive family history of CAD in these subjects. Hypertension was defined as BP ≥ 140/90 mm Hg on several occasions. Anthropometric assessment was done which included Height (meter), Weight (kilogram) and calculation of Body mass index (BMI) = Wt (kg)/ Ht (mt2). Obesity was defined as BMI ≥25kg/m^2 as for Asians [www.diabetes.com.au/pdf/obesity_report.pdf]. A detailed history, clinical examination was recorded for all study subjects.

After an overnight fast (minimum 12 hours), 2ml of peripheral venous blood was collected from anti cubital vein using a dry, disposable syringe under sterile conditions in a sterile plain vial. Serum was separated by centrifugation at 3000 rpm for 15 minutes. Fresh serum was used for estimation of total cholesterol, HDLC and TG. The tests were carried out in an automated clinical chemistry autoanalyzer (Beckman) using standard reagents/ kits (Randox laboratories).

The following tests were done as part of **routine lipid profile**:

Serum Total cholesterol (TC) [9].

Serum Triacylglycerol (TG) [10].

Serum HDL cholesterol (HDLc) [11].

Serum LDL cholesterol (LDLc) calculated using Freidwald formula [12].

The **Atherogenic ratios** were calculated as follows:

Atherogenic Index of Plasma (AIP) = log TG/HDLc

Castelli's Risk Index (CRI-I) = TC/HDLc

Castelli's Risk Index (CRI-II) = LDLc/HDLc

Atherogenic Coefficient (AC) = (TC– HDLc)/HDLc

Statistical analyses were performed with the SPSS version 20.0 software programme. For comparison of variables with a normal distribution unpaired, 2-tailed Student's t-test and Pearson's correlation were used, whereas the Mann–Whitney U-test was used for variables with a skewed distribution to analyse clinical and laboratory data. A $p \leq 0.05$ was considered statistically significant.

RESULTS

The study population characteristics are described in **Table 1**. The present study was designed to assess the use of specific ratios derived from routinely done basic lipid profile parameters in the identification of individuals at risk for CAD. Case and control groups were age and sex matched. Obesity and hypertension were the most significant risk factors observed in the patients of CAD. BMI was found to be significantly higher in cases as compared to the control group (25.96±0.45 vs 24.46±0.31 kg/m^2).

The results of lipid profile and lipid ratios are given in **Table 2**. CAD patients had statistically significant increase (p=0.005) in TG and a statistically significant decrease (p=0.001) in HDLC. No significant difference

was observed in TC and LDLC levels between the study groups. All the calculated ratios were found to be significantly elevated in cases as compared to controls.

As seen in **Table 3**, regression analysis showed all the four ratios to be significantly contributing to the risk of CAD, with AIP contributing 31% to the total risk, CRI-I 20%, CRI-II 13% and AC 17% to the total variations in CAD patients. All the ratios were found to be significantly positively correlated with CAD.

Table 1: Characteristics of Study Population

		Cases	Controls	p value
Age[b]		54.36±1.62	51±1.51	0.45
Sex	Male	64%	62%	
	Female	34%	38%	0.83
Risk factors	Obesity	64%		
	hypertension	56%		
	Smoking	48%		
	DM	16%		
BMI(kg/m^2)[b]		25.96±0.45	24.46±0.3	0.007[a]

[a]p value ≤ 0.05 is considered statistically significant
[b]Values are expressed as Mean ± S.E.M (Standard Error of Mean)

Table 2: Lipid profile and ratios among study groups

Lipid profile (mg/dl)	Cases[b]	Controls[b]	p value
TC	147.6±5.3	154.6±3.7	0.3
TG	140.6±6.3	119.6±3.8	0.005[a]
HDLc	27.8±0.9	42.1±0.6	0.001[a]
LDLc	89.1±4.3	86.2±3.4	0.6
Non HDLc (TC-HDLc)	119.8±4.4	112.5±3.1	0.5
Lipid ratios			
[c]AIP	0.39±0.03	0.09±0.02	<0.001[a]
[e]CRI-I	5.48±0.23	3.80±0.16	<0.001[a]
[e]CRI-II	3.18±0.16	2.37±0.14	<0.001[a]
[d]AC	4.48±0.23	3.07±0.16	<0.001[a]

[a]p value ≤ 0.05 is considered statistically significant
[b]values are expressed as Mean±S.E.M (Standard Error of Mean)
[c]AIP: Atherogenic index of plasma
[d]AC: Atherogenic coefficient
[e]CRI: Castelli's Risk Index

Table 3: Pearson's Coefficient of Determination in CAD cases

Parameters	Coefficient of correlation (r)	Coefficient of determination (R^2)
[a]AIP	0.56	0.31
[b]CRI-I	0.45	0.2
[b]CRI-II	0.37	0.13
[c]AC	0.41	0.16

[a]AIP: Atherogenic Index of Plasma; [b]CRI: Castelli's Risk Index; [c]AC: Atherogenic Coefficient

DISCUSSION

Lipid profile refers to some routinely done biochemical tests to assess the atherogenic status of individuals at risk of coronary artery disease (CAD). It includes serum triacylglycerol (TG), serum total cholesterol (TC) and its sub fractions like HDLc and LDLc. The Framingham heart study over years has established the role of deranged lipid profile in the progression of CAD and deranged LDLc levels are the primary target for treatment [13]. Calculating certain ratios using these parameters especially in situations where LDLc levels are below target range may increase the identification of at-risk individuals. Hence, this study aimed at evaluating the role and contribution of the ratios like Atherogenic Index of Plasma (AIP), Castelli's Risk Index I & II (TC/HDLc and LDLC/HDLc; respectively) and Atherogenic Coefficient (AC) in CAD.

In this study, most of the subjects were in the age group of 40-45 yrs with 62% males and 34% females. BMI was found to be significantly different between the two groups with most of the patients being obese. We found that the mean levels of serum TG were significantly higher in case group (140.60 ± 44.62 mg/dl) as compared to controls (119.62 ± 26.64 mg/dl). The mean serum HDLc levels were significantly lower in case group as compared to controls ($p<0.05$). As obesity was found to be the predominant risk factor in our case group, the deranged TG and HDLc levels may be attributed to it. Obesity is characterised by insulin resistance, so enhanced fatty acid esterification is observed due to elevated insulin levels and serum TG raises [14]. Moreover, the decrease in HDLc levels is due its enhanced catabolism.

CAD has been associated with alterations in lipid metabolism, which include hyper-triglyceridemia and significantly reduced HDLc [15]. The latter is considered an independent risk factor for increased susceptibility to CAD [16]. The pattern observed in our study is very characteristic of dyslipidemia observed in Indians as obesity is rampant owing to lifestyle problems [2]. But in this study, serum TC and LDLc did not show any significant difference between the two groups. TC was found to be below 200 mg/dl in 74% patients and LDLc was below 130 mg/dl in 86% patients of CAD. Moreover, it has been observed that obesity leads to rise in levels of small dense LDLc particles which are not measured routinely. Atherogenic lipoprotein phenotype is characterised by high TG, low HDLc and rise in small dense LDLc [14]. In such a scenario, it is essential to go beyond the routinely done lipid profile; especially, in centres with insufficient resources and owing to high cost of mostly available tests, these lipid ratios may prove a boon in the patient management.

On evaluation of lipid ratios, in the current study, we observed that Atherogenic Index of Plasma (AIP) was significantly higher in cases as compared to controls ($p < 0.001$). AIP is a ratio calculated as (logTG)/HDLc. Studies have shown an inverse relationship that exist between TG and HDLc and that the ratio of TG to HDLc is a strong predictor of infarction [17]. AIP is being used by some practitioners as a significant predictor of atherosclerosis. It has been suggested that AIP values of -0.3 to 0.1 are associated with low, 0.1 to 0.24 with medium and above 0.24 with high Cardiovascular risk [18]. As TG and HDLc were both deranged in our case group so we were expecting AIP to be significantly raised. We observed AIP ratio of 0.39 in cases and 0.09 in controls which are in concordance with the suggested cut-offs. Moreover, studies have shown that in situations where other atherogenic risk parameters like TG and HDLc appear normal, AIP may be the diagnostic alternative [19]. Studies have shown its role in predicting cardiovascular risk and effectiveness of therapy [20].

Castelli's Risk Ratio (CRI) is based on three important lipid profile parameters i.e. TC, LDLc and HDLc. CRI-I calculated as the ratio of {TC/HDLc} and CRI-II as {LDLc/HDLc} [21], was found to be significantly higher in cases compared to controls ($p<0.001$). In our study, we could not observe a significant difference in TC and LDLc levels between the two study groups whereas, the ratio based on these parameters showed a significant difference between the two groups. This clearly suggests the relevance of ratios over individual lipid parameters especially in situations where the drug management might be affected. In this study, the two main targets of starting drug therapy in at risk individuals' i.e LDLc and TC were both below target range. But based on the significance of the ratios, the desired actions may

be initiated. The Canadian working group had chosen the TC/HDLc ratio as a secondary goal of therapy considering it to be a more sensitive and specific index of cardiovascular risk than total cholesterol, particularly in individuals with TG>300mg/dl [22]. We observed CRI-I in our case group was > 4 in concordance with other studies [23]. Studies have shown the association of TC/HDLc ratio with coronary plaques formation [24]. In our study, CRI-II was also found to be above the upper limit for normal range i.e. >3 as observed in other studies [23]. In PROCAM study, it was observed that subjects with LDLc/HDLc >5 had six times higher rate of coronary events [25].

Atherogenic Coefficient (AC), calculated as {(Non-HDLc)/HDLc} or {(TC-HDLc)/HDLc} is a measure of cholesterol in LDLc, VLDLc, IDLc lipoprotein fractions with respect to good cholesterol or HDLc. It reflects atherogenic potential of the entire spectrum of lipoprotein fractions. Non HDLc is the second target of therapy after LDLc as per ATPIII guidelines especially in individuals with hyper-triglyceridemia [13]. Studies have shown Non-HDLc being similar to Apo-B in assessing atherogenic cholesterol and lipoprotein burden [26]. In our study, this ratio based on Non-HDLc was found to be significantly higher in cases as compared to controls ($p<0.001$), even when there was no statistically significant difference observed between Non-HDLc among the two groups.

On performing regression analyses, we found that AIP contributes maximum among the four ratios, approx. 30% to the risk of developing CAD. This study suggests that in patients with hyper-triglyceridemia, CRI-I becomes the major predictor of the disease contributing 20% in identification of at risk individuals followed by AC with 16% and CRI-II with 13% contribution to the total risk of CAD.

CONCLUSION

The aforementioned observations suggest that lipid ratios like Atherogenic Index of Plasma, Castelli risk index and Atherogenic coefficient could be used for identifying individuals at higher risk of cardiovascular disease in Indian population in the clinical setting especially when the absolute values of individual lipoproteins seem normal and in individuals with elevated TG concentrations. These can be easily calculated from the routinely done lipid profile parameters especially in centres where new tests are not possible due to cost factor. Thus, the use of these indexes should be encouraged to complement the existing profile of tests for identifying high risk individuals for CAD and effective drug management.

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