Atherogenic Index of Plasma (AIP) As a Parameter in Predicting Cardiovascular Risk in Males Compared To the Conventional Dyslipidemic Indices (Cholesterol Ratios)

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Abstract

Background: Several indices had been derived from lipid profiles to establish an index for predicting the risk of having coronary event. The atherogenic index of plasma, is a strongly emerging index that is now fulfilling the criteria to be used as a standalone index for cardiac risk stratification.

Objectives: To find out whether the atherogenic index of plasma, was superior to the conventional daily used atherogenic indices in predicting cardiac risk.

Subjects and methods: A case-control study in which 119 males with an age range of (43-68) years and with acute myocardial infarction together with 97, apparently healthy males of matched age were enrolled. For each participant, a fasting lipid profile done and the following atherogenic indices were calculated: (total cholesterol / high-density lipoproteins), (high-density lipoproteins / low-density lipoproteins), (low-density lipoproteins / high-density lipoproteins), and the (atherogenic index of plasma). The indices were compared in both groups and then in the patients group to figure out which index has yielded the highest sensitivity in predicting the risk of having coronary artery disease.

Results

- All of the atherogenic indices were found to be significantly different upon comparing these indices in both patients and control groups. Where the P value was (0.0001) for (TC/HDL), (HDL/LDL), and (AIP); and it was (0.0026) for (LDL/HDL).
- AIP was found to have the highest sensitivity for predicting atherogenicity among the other atherogenic indices with a value of 84% versus 68%, 73%, and 76% for (TC/HDL), (HDL/LDL) and (LDL/HDL) ratios respectively.

Conclusions: The AIP was a superior index for predicting the coronary arterial disease when compared to the most commonly used indices of atherogenicity in every day practice.

Keywords*:* Atherogenic index of plasma, Coronary heart disease, Atherogenic indices.

الخلاصة

المقدمة: تم اشتقاق مؤشرات عدة من دهون الدم لإنشاء مؤشر للتنبؤ بخطر وجود تصلب الشرايين التاجية. ان مؤشر تعصد البلازما، هو مؤشر ناشيء بقوة بعد أن استوفى المعايير التي تؤهله للاستخدام كمؤشر مستقل للتنبؤ بمخاطر القلب.

الهدف: لمعرفة ما إذا كان مؤشر معصد البلازما، متفوقا على المؤشرات التقليدية في توقع خطر تصلب الشرايين في القلب.

الطرق: شملت هذة الدراسة 119 ذكرا تراوحت أعمارهم (43-68) سنة، من المصابين باحتشاء عضلة القلب الحاد مع 97 من الذكور الاصحاء من العمر المتطابق. لكل مشارك، تم قياس مستوى الدهون الصيامي وحسبت مؤشرات التعصد التالية: (الكوليسترول الكلي / الدهون عالية الكثافة)، (الدهون عالية الكثافة / الدهون منخفضة الكثافة)، (الدهون منخفضة الكثافة / الدهون عالية الكثافة)، و (ان مؤشر تعصد البلازما) وتمت مقارنة المؤشرات في كل من المجموعتين ثم في مجموعة المرضى لمعرفة أي مؤشر قد حقق أعلى حساسية في توقع خطر وجود تصلب الشريان التاجي.

النتائج:

- ان جميع جميع مؤشرات التعصد كانت مختلفة بشكل كبير بعد مقارنة هذه المؤشرات في كل من مجموعة المرضى

والمجموعة الضابطة .حيث بلغت القيمة الاحصائية (0.0001) لكل من (TC / HDL)، (HDL / LDL)، و(AIP) ، وكانت (0.0026) لل (LDL / HDL)
- وجد AIP أعلى حساسية للتنبؤ بالتعصد بين المؤشرات الأخرى بقيمة بلغت 84٪ مقابل 68٪، 73٪، و 76٪ لل (TC/HDL)، (HDL/LDL) و(LDL/HDL) على التوالي.
الاستنتاجات : كان مؤشر AIP متفوقا للتنبؤ بمرض الشريان التاجي بالمقارنة مع بقية المؤشرات.

Introduction

Despite considerable advances that happened during the past decades, there is increasing awareness among scientists, epidemiologists, and clinicians that current approaches to evaluation of coronary heart disease (CHD) risk in asymptomatic individuals remain suboptimal [(1)]. There is also controversy around recommending widespread use of additional metabolic markers, such as apolipoprotein (APO) levels, indices of fibrinolytic activity and of susceptibility to thrombosis (e.g., plasminogen activator inhibitor-1 and lipoprotein[a] levels), markers of inflammation (e.g., C-reactive protein levels), and markers of insulin resistance (waist circumference and fasting insulin levels). Although all of these markers have been shown to predict CHD events, whether these variables contribute to CHD risk independently of the variation in traditional risk factors and lipid variables remains a matter of debate. Regarding the traditional fasting plasma lipid profile (triglycerides [TGs], total cholesterol [TC], low-density lipoprotein cholesterol [LDL] [which is most often calculated rather than measured directly], and high-density lipoprotein cholesterol [HDL]), there is no universal acceptance of how this information should be used and interpreted, although several consensus documents have been produced [(2-6)]. Because there is overwhelming evidence that an elevated LDL concentration in plasma is atherogenic [(7 and 8)], whereas a high HDL level is cardioprotective [(9-11)], the measurement and interpretation of LDL and HDL levels is emphasized in the US National Cholesterol Education Program (NCEP) guidelines [(4)]. According to these guidelines, LDL concentration should be considered the primary therapeutic target, whereas HDL levels may also be critical in the assessment of CHD risk. Thus, because TG levels are ignored in the National Cholesterol Education Program algorithm (NCEP), the clinician is left with LDL and HDL levels to assess risk while considering the presence or absence of other important risk factors, such as family history of early CHD, age, smoking, hypertension, diabetes mellitus, low physical activity, and obesity. On this basis, the LDL/HDL ratio is often calculated to estimate CHD risk. Results of prospective studies [(12 and 13)] have suggested that a high LDL/HDL ratio combined with hypertriglyceridemia is associated with highest CHD risk. Thus, algorithms have been produced showing that an elevated LDL/HDL ratio combined with elevated TG is associated with high CHD risk. This dyslipidemic state (lipid triad) has been described as atherogenic dyslipidemia. [(14)] This approach was further simplified by using the TC/HDL ratio. Because there is more cholesterol in the very LDL (VLDL) fraction in individuals with elevated TG concentrations, the LDL/HDL ratio may underestimate the magnitude of the dyslipidemic state in these patients. On that basis, there was a proposal that the high prevalence of moderate hypertriglyceridemia among patients with CHD explains why the TC/ HDL ratio was the best till now established predictor of ischemic heart disease (IHD) risk in several observational prospective studies. [(15)]

Therefore, the objective of this study was to present evidence that supports the notion that the Atherogenic Index of Plasma (AIP) ratio may be a better and simpler cumulative marker of the presence of atherogenic dyslipidemia and of increased IHD risk than the classical

cholesterol ratios since it takes in count the underestimated role of triglycerides in the process of atherogenisity. It is now generally accepted that both elevated levels of non-high-density lipoprotein cholesterol and low (HDL) concentrations may promote the development of atherosclerosis. This is supported by data from the Framingham study, [16] which showed that as the ratio of total cholesterol/HDL (TC/HDL) increases, so does the risk of coronary heart disease (CHD). In populations with low CHD incidences, average values of TC/HDL are below 4.0. TC/HDL ratio is a superior measure of CHD risk than non-HDL cholesterol. It captures the protective effect of HDL cholesterol as well as the harmful effects of non-HDL cholesterol. [17] The current NCEP guidelines recommend levels of LDL and HDL that represent a ratio of about 2.5 [18]. Current researches suggest risk of death from cardiovascular disease begins to increase significantly around a ratio of 3.3–3.7 [19]. The existing focus on LDL as the primary culprit in atherogenesis may divert attention from the more efficient lipid profile of LDL/HDL. The LDL/HDL ratio reflects the two-way traffic of cholesterol entering and leaving the arterial intima in a way that the individual levels of LDL and HDL do not [20]. The HDL/LDL ratio looks at the ratio of good cholesterol (HDL) to bad cholesterol (LDL). The ratio is determined by dividing the HDL cholesterol into the LDL cholesterol. For example, if a person has HDL cholesterol of 50 mg/dL and LDL cholesterol of 150 mg/dL, the HDL/LDL ratio would be 0.33. The goal is to keep the HDL/LDL ratio above 0.3, with the ideal HDL/LDL ratio being above 0.4. [21] The atherogenic index of plasma was established in an attempt to predict cardiovascular risk. AIP is based on the ratio of the values of triglycerides to high-density lipoprotein (HDL) levels, and is calculated according to the following formula (AIP=Log [TGs]/ [HDL]) where both of them are measured in the plasma and are expressed in molar concentration. When placed into the scope of AIP, both the triglycerides and the HDL refer to the true relationship of atherogenic lipids to protective lipids. The AIP has demonstrated cardiovascular risk in several clinical trials the optimal value for AIP should be less than 0.1. [22]

Subjects and Methods

This was a case-control observational study that involved the enrollment of 119 male patients with an established diagnosis of acute myocardial infarction (AMI) admitted to the CCU of Al-Hussein general hospital/ Kerbala/ Iraq, during the period from the 1st of October 2008 to the 30th of March 2009. Ninety-seven apparently healthy subjects were also included in this study as a control group. Any patient with one or more of the below criteria was excluded from the study:

1- Triglycerides level of greater than 399 mg/dl.
2- Failure to fast lipid free diet for more than 8 hours.
3- Taking any kind of lipid lowering therapy prior to admission.

After participants had fasted for 8-12 hours, blood samples were collected from the median cubital vein while participants were sitting or reclining. A tourniquet was used, but it was released just before the withdrawal of blood into a sterile light green top PST "*Plasma Separator Tube*" where the interior of the tube is coated with sodium heparin as anticoagulant. Plasma was separated from blood by centrifugation at 3000 RPM for 5 minutes and stored frozen at −20° C and the analysis was carried out within one week of sample collection. Plasma TC, HDL, and TG concentrations were determined using Aquarius CE 7500 analyzer by Cecil Instruments Ltd. Milton Technical Centre, Cambridge, England. Total cholesterol was measured using established enzymatic methods of Allain *et al* [23] with the Randox cholesterol kit (*Randox England*).

HDL was estimated by HDL precipitant method [24]. Triglyceride was assessed enzymatically [25]. LDL was calculated using the Friedewald formula [26]. VLDL was calculated based on the formula VLDL=TG/2.2 [27]. Lipid profiling was conducted on samples that were obtained during the first 24 hours of admission to avoid the erroneous results that come from the fact that 24 hours after AMI, serum or plasma levels of cholesterols and triglycerides alter significantly and they may take several weeks to revert to normal levels [28]. The principle of the method for measuring total cholesterol involves the use of three enzymes: Cholesterol Esterase (CE), Cholesterol Oxidase (CO) and Peroxidase (POD). In the presence of the former the mixture of phenol and 4-aminoantipyrine (4-AA) are condensed by hydrogen peroxide to form a quinoneimine dye the intensity of which is proportional to the concentration of cholesterol in the sample [23]The HDL measuring technique uses a separation method based on the selective precipitation of apoliprotein B-containing lipoproteins, namely, (VLDL, LDL and (a) Lpa) by the use of phosphotungstic acid/$MgCl_2$, then the sedimentation of the precipitant by centrifugation and subsequent enzymatic analysis of HDL, as it will be the only residual cholesterol remaining in the clear supernatant. [24] The principle of the method for measurement of triglyceride is that sample triglycerides incubated with lipoprotein lipase (LPL), liberate glycerol and free fatty acids. Glycerol is converted to glycerol-3-phosphate (G3P) and adenosine-5-diphosphate (ADP) by glycerol kinase and ATP Glycerol-3-phosphate is then converted by glycerol phosphate dehydrogenase (GPO) to dihydroxyacetone phosphate (DAP) and hydrogen peroxide (H_2O_2). In the last reaction, hydrogen peroxide reacts with 4-aminophenazone (4-AP) and p-Chlorophenol in the presence of peroxidase (POD) to give red colored dye the intensity of which is proportional to the triglycerides concentration in the sample. [25] The LDL concentration was estimated using the equation of Friedewald *et al* [26] because men with TG concentrations greater than 399 mg/dL (4.5 mmol/L) were excluded from the analyses since this equation is not applicable in those with TG levels greater than 400 mg/dl.

Statistical analysis

Statistical analysis was performed by using the least significant differences (LSD) post Hoc test to identify the group (s) responsible for statistical differences following student paired t-test, utilizing (SPSS version-16) and (Excel-2010) softwares. All values were expressed as Mean ± SD. Results with P value of less than 0.05 considered to be statistically significant.

Results

Table-1 gives the baseline characteristics of the 115 male patients with AMI compared with those of the 97 healthy subjects control group. Overall, the patients group was characterized by an unfavorable metabolic profile compared with men of the control group.

After comparing patients with the controls and establishing the abnormality in lipid profiles and atherogenic indices between both groups, the indices of the patients themselves were compared with each other and accordingly, the results are shown in table-2.

Discussion and conclusions

The results of this study showed that the patients had abnormal lipid profiles when compared to the controls as shown in table-1 where the TC, LDL-C and TGs were all significantly higher in patients than controls group with a (***p value*** < 0.0001, and the HDL-C was significantly lower (***p value*** < 0.0001). Likewise, the

atherogenic indices were found to be significantly different in the patients group with (***P value*** < 0.0001) for (TC/HDL), (HDL/LDL), and (AIP); and of (0.0026) for (LDL/HDL). These abnormalities in the patient's lipid profiles probably, contributed to the development of CHD.

Table 1. the results of comparison of different parameters between both patients and control groups

Variable	Patients (n=119)	Controls (n=97)	P value †
Age	57 ± 6	56 ± 2	0.0771
Total cholesterol	214.4 ± 43.83	192.32 ± 45.18	< 0.0001
HDL	42.33 ± 16.93	53.92 ± 11.2	< 0.0001
LDL	130.22 ± 42.35	87.95 ± 32.33	< 0.0001
Triglycerides (TG)	211.18 ± 93.63	123.46 ± 54.4	< 0.0001
Total cholesterol/HDL ratio	5.73 ± 2.34	3.81 ± 1.68	< 0.0001
HDL/LDL ratio	0.21 ± 0.11	0.41 ± 0.09	< 0.0001
LDL/HDL ratio	4.59 ± 1.89	2.96 ± 1.35	0.0026
AIP	0.33 ± 0.25	0.9 ± 0.18	< 0.0001

- All values are expressed as mean + standard deviation unless mentioned elsewise.
- † P value of 0.05 or less considered to be statistically significant.

Table 2. the comparisons of both sensitivity and specificity among different atherogenic indices

Index	*Sensitivity*	*Specificity*	*C.I. of sensitivity*	
			Lower limit	*Upper limit*
TC/HDL	0.68	0.98	0.61	0.75
HDL/LDL	0.73	0.99	0.65	0.80
LDL/HDL	0.76	0.99	0.68	0.82
AIP	0.84	0.99	0.76	0.89

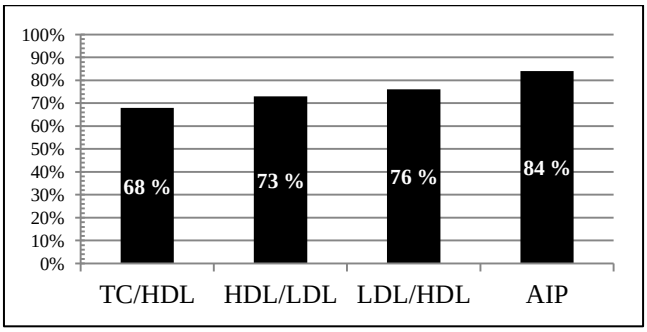

Figure 1. the respective sensitivity of each index for correlating with AMI.

These observations are compatible with those of other studies where abnormal lipid profile were observed in CHD cases and is regarded as independent risk factors in the patho-mechanism of atherogenesis [(29)]. The study also showed that AIP resulted in the highest sensitivity when compared with the other three atherogenic indices where its value of sensitivity was 84% versus 68%, 73%, and 76% for total cholesterol/HDL, HDL/LDL and LDL/HDL ratios respectively as illustrated in figure-1. These results are consistent with those of Gaziano *et al* reported that

"the ratio of triglycerides to HDL was a strong predictor of myocardial infarction" [30]. Isolated elevation in triglycerides increases CHD risk, but its effect can be counteracted by the levels of HDL-C [31]. The atherogenic index of plasma been successfully used as an additional index when assessing cardiovascular (CV) risk factors [32, 33]. Indeed, 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 CV risk [34], and thus according to the findings of this study, male patients were are at a high risk of developing CHD. It has been demonstrated that the development of CHD is a function of the particle size of LDL-C and HDL-C, with the small particle size exhibiting great atherogenic potential [35]. Indeed, cholesterol etherification rate in HDL-C plasma (FER_{HDL}) has a strong relationship between lipoprotein particle sizes and thus can be considered as a functional risk marker for CHD [32, 33]. More recently, researchers have shown that the logarithmically transformed TG/HDL-C ratio is the best determinant for (FER_{HDL}) and thus a better predictor of cardiovascular risk than other previously used lipid parameters [36]. Furthermore, in situations where other atherogenic risk parameters appear normal, AIP may be the diagnostic alternative [37].This study concludes that atherogenic index of plasma was an index of highest sensitivity for predicting the acute coronary events and combined with the fact that it is available and easy to calculate candidates it as a better screening tool for evaluating the cardiac risk and therefore it is recommended that

1- AIP is recommended to be used as a predictor of CHD.
2- It should be used as a monitoring index for any lipid lowering intervention.
3- Further studies required to improve these results in a larger sample size and correlating AIP with angiographically proven CHD.

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