Original Article

Evaluating the utility of plasma Atherogenic Index among several atherogenic parameters in patients with chronic renal Failure on maintenance hemodialysis

Wafa F. Al-Tai* **Bsc.Msc.Phd.Biochem**
Elham M. H. Jaffer* **Bsc.Msc.Biochem**
Zean A. Ali** **Bsc.Msc.Phd.Biochem**

Summary:

Background: Patients with chronic renal failure undergoing longterm hemodialysis (HD) are prone to atherosclerosis and at increased risk of developing cardiovascular diseases.

Objective: The objective of this study is to compare atherogenic index of plasma (AIP) in predicting the risk of cardiovascular disease (CVD) in patients with chronic renal failure (CRF) on regular hemodialysis, when associated with other chronic diseases.

Patients and methods: A total of forty male patients with CRF on hemodialysis, matched in, age, body mass index BMI, and duration of hemodialysis were enrolled. They were grouped as group 1 (G1) includes eleven subjects with CRF without (hypertension and / or diabetes) groups 2 (G2) fourteen CRF subjects with hypertension and group 3 (G3) fifteen CRF subjects with diabetes. As a control group, eighteen healthy male subjects were included with special exclusion criteria. The plasma total cholesterol TC, triglyceride TG, and high density lipoprotein-cholesterol HDL-C were estimated using spectrophotometry methods. While low density lipoprotein-cholesterol LDL-c, and AIP were calculated using special formulas. Statistical analysis was performed by the student t-test.

Results: The results of the study revealed significant increase in TC and TG, with significant decrease in HDL-c for all patient groups compared to control. No significant difference in LDL-c of G1 compared to control was found, while significant increase in LDL-c of G2 and G3 was found when compared to G1 or control. The AIP values were (0.42 ± 0.19 vs 0.43 ± 0.17; $P>0.05$) for G1 and G2 respectively, that showed no significant difference of atherogenic risk between these groups.

Conclusions: These results concluded that AIP seems to be superior to LDL-c in predicting the risk for CVD in CRF groups on hemodialysis and those at the highest risk when CRF coupled with diabetes.

Keywords: AIP: atherogenic index of plasma, CRF: chroic renal Failure, hemodialysis.

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Introduction:

Chronic Renal Failure CRF refers to an irreversible deterioration in renal function which classically develops over a period of years. It may be caused by any condition that destroys the normal structure and function of the kidney(1). An initial insult to the kidney function and further loss of nephrons to the point where the person must be placed on dialysis treatment or transplanted. This condition is referred to end stage renal disease (ESRD). The frequency and severity of CRF are greatly increased by concurrent hypertension or diabetes mellitus (2). Charles and terry in (2008) proved that abnormalities in lipid metabolism occur in patients with CRF (3). Serum lipid profile investigation usually consists of Total Cholesterol TC, Triglyceride TG, Low density lipoprotein LDL-c and High density lipoprotein HDL-c measurements. Lipoproteins enable lipids like cholesterol and triglyceride to be transported within the water-based bloodstream (4). Mathematically estimated value of serum LDL-c is commonly used to estimate how much LDL-c is driving progression of atherosclerosis (5). Frequently a risk assessment for cardiovascular disease CVD is given by comparing the total cholesterol to HDL-c ratio (6). Atherogenic lipoprotein profile of plasma is an important risk factor for CVD. It is characterized by high ratio of LDL-c to HDL-c. Atherogenic index of plasma AIP is the new marker of atherogenicity, AIP is the ratio calculated as log TG/HDL-c. Existence of hypertriglyceridemia will increase the activity of hepatic lipase HL which results in the increase of HDL-c catabolism (degradation of HDL-c). Each degradation of 1mg HDL-c will correlate with 2% increase in the risk coronary heart disease CHD (7,8). This study was designed to evaluate the most sensitive predictive parameter among AIP in Chronic Renal Failure CRF on hemodialysis. TC/HDL-c ratio and LDL-c/HDL-c ratio is predicting atherosclerosis in patient with CRF who are on hemodialysis with and without complication ,(hypertention or diabetes).

**Chemistry department/College of Education Ibn Al-Haitham/ Baghdad University.*
***Chemistry department/College of Education- Scientific Departments / Salahaddin University.*

Patients and Methods:

Forty male patients, with CRF (non smokers and non alcoholics), age, and body mass index BMI matched, who attended different hospitals including (Ibn Albetar hospital, Baghdad teaching hospital and Kadumia teaching hospital in Baghdad) for regular hemodialysis (i.e two times weekly, each for two hours) were included in this study. The patients were grouped according to reason of the CRF, or to its complication as: Group I (G1) consisted of CRF male patients of unknown cause (n=11) Group II (G2) consisted of CRF male patients with hypertension (n=14) Group III (G3) consisted of CRF male patients with diabetes mellitus (n=15) Eighteen Age and BMI matched healthy males were also enrolled in this study as control group. They had no evidence of heart disease, hypertension, diabetes mellitus, kidney disease, and hepatic failure. Also smoker, alcoholics, and subjects taking a lipid lowering agents were excluded. Three milliliters of blood was droun from all participants after an overnight fast (>12 hours). The blood was placed in tube containing EDTA, centrifuged at 3500 rpm for ten minutes to separate plasma from erythrocytes. The plasma was stored at -20˚C in aliquot liquated and used for lipid profile analysis. The BMI was calculated as the weight (Kg) divided by the height in (m^2). The AIP was calculated as log (TG/HDL-c) using the Czech online calculator of atherogenic risk.(7) Parmeters of plasma lipids were performed using ready kits from Bio- Merieux A.S., France as follows: Plasma HDL-c was determined after precipitation of chylomicron, VLDL-c and LDL-c contained in the plasma sample by the addition of phosphotungestic acid solution, the supernatant obtained after centrifugation contains the HDL-c, from which the TC was determined. Plasma triglyceride TG was determined colorimetrically by TG enzymatic method using a series of enzymes (i.e. lipase, glycerokinase, glycerol-3-phosphate oxidase and peroxidase). (6) Plasma LDL-c was estimated indirectly by using the Friedewaled formula.(9)

Statistical analysis:

Comparison of each lipid parameter, ratio of TC/HDL-c, ratio of LDL-c/HDL-c and AIP levels between each patient group and control, also between patient groups were analyzed using student-t-test, significant variation is considered when P value is < 0.05.

Results:

Table (1) shows that all CRF groups are comparable in their BMI and age, and also with the control group. The hemodialysis duration of the three patient groups are comparable too. The result of the present study also revealed significant increase in TC and TG with a significant decrease in HDL-c in all patient groups when compared with control (table2). No significant change was noticed in LDL-c of G1 compared with control, on the other hand significant increase in LDL-c of G2 and G3 compared to the control group. Table (3) shows some differential analysis for predicting the risk of CVD in all patient groups compared to control is clear, while no significant difference between G1 and G2 was found. On the other hand the LDL-c/HDL-c ratio showed significant increase in G2 when compared to G1.

Discussion:

The obesity in men and women was a cause for high AIP, which predicts high blood pressure, diabetes, and vascular events (10). Therefore in this study the sex, age, and BMI were adjusted, so the risk ratio of CVD could be attenuated among group when the duration of hemodialysis was also adjusted. The results of this study as shown in table (2) are in agreement with some studies stated that all patients undergoing long term hemodialysis are likely to generate an increased arterial deposit, leading to atherosclerosis. Indeed, accelerated development of atherogenesis and a number of vascular episodes characterize patient with chronic renal failure subjected to hemodialysis(11). The increased risk of CVD has many causes, but dyslipidemia plays a prominent role in it, commonly associated with an abnormal lipoprotein phenotype which is characterized by increased TG, decreased HDL-c and an accumulation of small dense LDL-c particles even when the level of LDL-c are often normal(12). The high levels of Cholesterol Ch which was noticed in all patient groups compared to control could be explained on the bases that excess Ch is present in the form of LDL-c particles so called “bad Ch” to that in the form of Ch in the form of HDL-c referred as “good Ch”. The exact nature of the protective effect of HDL-c is not known; however, a possible mechanism is that serum esterase which degrades oxidized lipid is found associated with HDL-c. Possibly, the HDL-c associated protein destroys the oxidized LDL-c, accounting for HDL-c ′s ability to protect against heart disease. On the other hand oxidized atherogenic lipoprotein, namely oxidized LDL-c is taken up by immune system cells, which becomes engorged to foam cells. This foam become trapped in the wall of the blood vessels and contributes to the formation of atherosclerosis plaques that cause arterial narrowing and lead to heart diseases (13). A number of lipid related parameters have been used to predict the risk of coronary artery disease. According to Grover et al either the ratio of LDL-c/HDL-c or TC/HDL-c is the best related predictor of future cardiovascular events(14). Later TG/HDL-c was shown to be a more accurate predictor of heart diseases, the logarithmatically transformed ratio of plasma TG to HDL-c closely correlated with the LDL-c particle size and could serve as an indicator of the atherogenic lipoprotein phenotype(15). The value of AIP indicates a balance between the actual concentration of plasma TG and HDL-c, which predetermine the direction of the cholesterol transport in the intravascular pool (i.e the flux of newly produced cholesteryl esters by lecithin cholesterol acyltransferase) toward atherogenic

LDL-c or beneficial HDL-c (16). Clinical studies have shown that AIP predicts cardiovascular risk and that it is an easily available risk marker and a useful measure of the response to treatment(17). The results obtained by some researchers on 8394 subjects summarized data of AIP values increased with increasing cardiovascular CV risk, blood from young children have AIP below (0.1), while men and subjects with CV risk factors such as hypertension, diabetes, dyslipidemia, this value increased up to (0.4). Based on their data was suggested that AIP values of less than (0.1) are associated with low risk, (0.1 to 0.24) with medium risk and above 0.24 with high CV risk(18). In this study the AIP value for G3 was the highest this agrees with other studies claimed that, the AIP value increased significantly with increasing atherogenic risk AIP from 0.2 to 0.55 and in patient with diabetes, AIP was among the highest value(19). Recent studies revealed that hyperglycemia, dyslipidemia and perhaps to a lesser extent, hypertension which all contribute to the development of atherosclerosis (20, 21). It is well known that triglyceride-risk lipoproteins VLDL-c and LDL-c are atherogenic, and the occurrence of CVD has been shown to be related with the presence of negative correlation between hypertriglyceridemia and decrease in HDL-C value and increase in small dense LDL-c. These conditions are frequently found in type 2 diabetic patients (22). It has been reported that AIP has higher predicted value for atherosclerosis and some ratio of pro atherogenic markers when divided by HDL-c, will increase the odds ratio value which mean higher predictive value toward atherosclerosis, as compared to pro atherogenic markers alone(23,24). This study firstly, to the best of our knowledge, demonstrated that high values of AIP can serve as a significant predictor for future cardic events in CRF undergoing hemodialysis. From the present study, it is concluded that AIP and ratio TC/HDL-c are helpful for identifying high risk patients of CRF on hemodialysis patients with CRF and diabetes are at the higher risk, then CRF with hypertension, yet CRF without these complications (i.e diabetes and hypertension) are under less risk.

Table (1): Descriptive data of Chronic Renal Failure (CRF) male patient groups on hemodialysis and healthy controls.

Parameters	Control n=18	Group1 (G1) n=11	Group2 (G2) n=14	Group3 (G3) n=15
Age (years) mean±SD	43±8.1	49.3±7.3	48.3±9.3	54.3±9.5
BMI (Kg/m^2) mean±SD	25.3±2.8	26.7±3.1	25.2± 3.2	24.9±4.1
Duration of dialysis (month) mean±SD	------	12.3±2.1	12.2±3.5	14.7±4.3

Table (2): Lipid profile in plasma of CRF patient groups on hemodialysis and controls.

Lipid profile	Studied groups							P*		
Parameters	Control n=18	Group1 (G1) n=11	P	Group2 (G2) n=14	P	Group3 (G3) n=15	P	Group2 (G2) vs Group1	Group3 (G3) vs Group1	Group3 (G3) vs Group2
TC(mg/dL) mean±SD	187.3±13.2	201.7±48.1	S	234.3±50.3	S	287.9±46.2	S	S	S	S
TG (mg/dL) mean±SD	121.8±11.7	238.7±66.1	S	237.9±25.2	S	281.8±31.7	S	NS	S	S
HDL-c(mg/dL) mean±SD	49.8±8.3	39.1±11.7	S	40.2±13.8	S	37.7±17.7	S	NS	NS	NS
LDL-c(mg/dL) mean±SD	112.3±6.8	116.8±9.2	NS	146.2±7.8	S	152.3±11.8	S	S	S	NS

P values< 0.05 considered significant (S), and > 0.05 non significant (NS)
P values between the patient groups and control
P* values between the patient groups

Table (3): Differential analysis between AIP, Ratio of TC /HDL-c, and ratio of (LDL-c/HDL-c) in plasma of CRF patient groups on hemodialysis and controls.

Biomarkers of cardiovascular Risk	Studied groups							P*		
	Control n=18	Group1 (G1) n=11	P	Group2 (G2) n=14	P	Group3 (G3) n=15	P	Group2 (G2) vs Group1	Group3 (G3) vs Group1	Group3 (G3) vs Group2
AIP mean±SD	0.05±0.03	0.42±0.19	S	0.43±0.17	S	0.55±0.13	S	NS	S	S
TC/HDL-c mean±SD	3.74±0.08	5.95±1.73	S	5.90±1.39	S	7.70±2.35	S	NS	S	S
LDLc/HDL-c mean±SD	2.26±1.32	2.95±1.72	S	3.65±1.83	S	4.30±0.12	S	S	S	S

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