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Ischemia Modified Albumin and its Relation to Arterial Stiffness in Prevalent Hemodialysis Patient

Mohamed Saeed Hassan[1], Hesham Mohamed Atef Abouellail[1],

Dalia Abd Elfattah Abd Elfattah Mousa[2], Ashraf Hassan Abdelmobdy[*1]*

[1]*Internal Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt.*

[2] *Nephrology Department, Aga Central Hospital, Dakahlia, Egypt.*

Abstract

Patients with chronic kidney disease, particularly those on maintenance hemodialysis, especially had arterial stiffness risk. Ischemia Modified Albumin (IMA) is associated with increased oxidative stress and is thought to be a potential cardiovascular risk factor; hence, the researchers looked at the relationship between IMA and arterial stiffness, which is associated with an increased risk of vascular events. To study the association between IMA and carotid intima media thickness (CIMT) in end stage renal disease (ESRD) patients on maintenance hemodialysis. This study was conducted on 90 ESRD patients on maintenance hemodialysis. All patients were collected from Abo Elnomros hemodialysis unit, Giza governorate. After doing carotid Doppler, the patients were divided into: Group A: 60 patients with normal CIMT and Group B: 30 patients with increased CIMT. All the participants were subjected to: Complete history taking, complete clinical examination, and laboratory investigations (Urea before and after session, creatinine, complete blood picture, calcium, phosphorus, parathormone hormone, albumin, CRP, lipid profile), IMA levels, and CIMT measuring. There was a high significant positive correlation between IMA and CIMT (p-value **<0.001**) (r = 0.376) in the studied population. In the group A with normal CIMT, the median (IQR) of IMA were 120, (90-180) ng/ml, while in the group B with increased CIMT, it was 270, (110-300) ng/ml. IMA is a predictive marker of increasing CIMT as well arterial stiffness in hemodialysis patients. The most independent factors affecting IMA were CIMT, cholesterol and BMI. The cutoff value of IMA is >230ng/ml which might be used to differentiate between individuals with normal CIMT and individuals with increased CIMT implying the process of atherosclerosis.

Keywords: IMA, CIMT, ESRD, arterial stiffness.

Full length article **Corresponding Author*, e-mail: ashrafnephro@med.asu.edu.eg

1. Introduction

A changed form of serum albumin known as IMA is created when oxidative stress is present. This indicates oxidative damage on a systemic level [1]. Conditions including ischemia, hypoxia, acidosis, free radicals, and free iron can produce reactive oxygen species, which might hinder the N-terminus's capacity to bond with transition metals. As a result of hypoxia, acidosis, and the breakdown of the Na+–K+ pump that follows myocardial ischemia (MI), IMA is formed by the cleavage of the first two amino acids (Asp–Ala) of the HSA N-terminus. It is well known that IMA has poor affinity for binding transition metals [2]. Atherosclerosis is brought on by the accumulation of many atheromatous plaques, or cholesterol crystal deposits, in the inner layers of the arterial wall. These plaques have the potential to produce artery spasms or blockages, which can result in hypoxia and ischemia. A major contributing element to the onset and progression of systemic inflammation is increased oxidative stress, which coexists alongside it [3]. Free albumin in the circulation converts to IMA as a result of oxidative alterations and hypoxia/ischemia brought on by the constriction of arteries caused by atherosclerotic lesions [2]. IMA is produced as a result of modifications in albumin's ability to bind heavy transition metals, and its connection to atherosclerotic heart disease has been the subject of many investigations [4]. Another non-invasive measure that has gained popularity recently is called CIMT, and it may be used to track the development of cardiovascular disorders linked to atherosclerosis as well as early indications of the illness [5]. The underlying causes of this alteration in albumin structure have been proposed to include exposure to free iron and copper ions, hypoxia, acidosis, free radical damage, and disturbances of the sodium and calcium pumps. The precise

molecular process is yet unknown, though. However, MI reperfusion conditions are affected by each of these occurrences [6]. IMA is presently employed as a predictive indicator for acute coronary syndrome and MI. Obesity, hyperlipidemia, chronic renal disease, and DM are all associated with an elevated risk [7]. Researchers attempted to show a potential relationship between IMA and other cardiovascular risk factors as well as certain illnesses with higher occurrences of vascular events since IMA has recently been linked to increased oxidative stress and is thought to be a potential cardiovascular risk factor [8]. According to earlier reports, coronary artery disease is more common in individuals with chronic renal failure, and cardiovascular events account for the majority of mortality in this population. Nevertheless, hemodialysis patients with ESRD experience these episodes more frequently [6]. Sharma et al. [9] discovered a correlation between high IMA levels and a considerably bigger left ventricular size, poorer left ventricular systolic function, and higher mortality in ESRD patients. However, in hemodialysis patients, whether IMA is associated with arterial stiffness is not known [9-10]. Aim of the work was to study the association between IMA and CIMT in ESRD patients on maintenance hemodialysis.

2. Patients and methods

This cross-sectional study was conducted on 90 ESRD patients on maintenance hemodialysis for more than six months. All patients were collected from Abo Elnomros hemodialysis unit, Giza governorate in the period from December 2022 till August 2023. After doing carotid Doppler for more than 200 hemodialysis patients. **Patients were divided into:** Group (A): 60 patients with normal CIMT ≤ 0.8mm, and Group (B): 30 patients with increased CIMT > 0.8mm. Before the study began, all volunteers gave their informed permission after being educated about the purpose and advantages of the study.

2.1. Exclusion criteria

Diabetes mellitus, smoking, patients with active inflammatory diseases, patients receiving dialysis through hemodialysis catheters. Each patient was subjected to full history (age, sex, particular habits such as smoking, duration of dialysis, etiology of ESRD and drug history) and clinical examination (anthropometric measures including body weight (in kg) and patient height (in square meter) and assessment of body mass index).

2.2. Laboratory investigation

Blood samples were withdrawn immediately before midweek session (IMA, Urea before and after session, creatinine, complete blood picture, calcium, phosphorus, parathormone hormone, albumin, C reactive protein (CRP) and Lipid profile).

2.2.1. IMA levels

The kit measures the amount of Human IMA in samples using a double-antibody sandwich ELISA. The kit was obtained from Shanghai crystal day biotech ccompany (Shanghai, China). After pre-coating the enzyme well with Human IMA monoclonal antibody and allowing it to incubate, add biotin-labeled IMA antibodies and combine them with streptavidin-HRP to create an immunological complex. Repeatedly incubate and wash to eliminate any remaining uncombined enzyme. After adding Chromogen Solution A and B, the liquid's colour shifts to blue before eventually becoming yellow due to the acid's action. There was a positive correlation between the sample's Human Substance IMA concentration and colour Chroma.

2.2.2. Detection limit

2: 600 ng/ ml.

2.2.3. Measurement of CIMT

All carotid scans were performed with a carotid Doppler ultrasound scanner (GE logic F6) at the Abo Elnomros hemodialysis unit in Giza governorate. Patients were positioned in a supine posture with their neck hyperextended.

2.3. Statistical analysis

Revisions, codes, data collection, and entry into SPSS V. 23.0 were completed. Standard deviations, ranges, and the mean were the quantitative data's presentation format. Numbers and percentages were also used to represent qualitative characteristics. Chi-square and Fisher exact tests were used to compare groups using qualitative data rather of the X^2 test in cases where the predicted count in any given cell was less than 5. With the use of parametric distribution and quantitative data, the independent t-test was employed to compare two groups. To evaluate the relationship between two quantitative factors within the same group, Spearman correlation coefficients were employed. Five percent was the permitted error margin, while ninety-five percent was the confidence interval. Consequently, $P < 0.05$ is regarded as significant. The sensitivity, specificity, positive predictive value, negative predictive value, and AUC curve of the examined marker, IMA, were all measured using the ROC curve to determine the optimal cutoff point. The predictors of CIMT were evaluated using both univariate and multivariate logistic regression analysis.

3. Results

Table 1 show that weight and body mass index were significantly higher in group B. **Table 2** show that IMA was significantly higher in group B. There was significantly positive correlation between IMA and BMI, Total Cholesterol, and CIMT (Table 3 & figure 2). **Table 5** show that the independent factors affecting the level of IMA were cholesterol, BMI, and CIMT with p value (0.019, 0.048, 0.001) respectively**.** The best cutoff point for IMA was >230 with a sensitivity of 60%, a specificity of 90%, and an AUC of 77.1 % (Table 5 & figure 6). There was significantly positive correlation between CIMT and weight, BMI and IMA. Also, there was significantly inverse correlation between CIMT and creatinine (Table 6). The independent factors affecting CIMT were weight (P<0.006), IMA (P<0.001), and creatinine (P<0.007) (Table 7 and figure 1).

4. Discussion

Over 50% of deaths in hemodialysis patients are caused by cardiovascular and cerebrovascular disorders. Increased arterial stiffness has been shown to be a valid predictor of cardiovascular morbidity and mortality in dialysis patients [10]. For individuals with ESRD,

cardiovascular disease (CVD) is the primary cause of mortality. These individuals have cardiovascular mortality that is 10–20 times greater than the normal population. Measurements of carotid artery IMT have been shown to be beneficial in predicting long-term mortality in these patients, according to Koch et al. [11] and Kato et al. [12]. A helpful and noninvasive method to evaluate arterial stiffness is IMA. It has been proven that IMA plays an independent effect in determining cardiovascular and all-cause mortality in patients receiving hemodialysis [13]. In this cross-sectional study, we studied the association between IMA and CIMT in hemodialysis patients. According to our research, there was a statistically significant difference in weight and BMI between the groups under examination. These results are consistent with those of earlier studies that revealed that participants who were overweight had greater IMT compared to subjects who were normal weight, and that subjects who were obese had higher IMT compared to patients who were underweight and normal weight [14]. Table 1 (1). These findings imply that some of the consequences of obesity on carotid anatomy may be significant risk factors for carotid atherosclerosis [15]. However, our study disagreed with Jiao et al. [10] and Zheng et al. [16], as they had no statistically significant difference in BMI between the studied groups. Concerning IMA, the median was significantly higher (270 ng/ ml) in patients with an increased CIMT (group B) with highly significant p value (p=0, 0001) Table (2) and figure (3). This finding was consistent with a research by Montagnana et al. [17], who used IMA to diagnose ACS in hemodialysis patients and came to the conclusion that IMA may be used to accurately stratify these patients' long-term risk. Sharma et al. [9] found a strong link between IMA levels and unfavourable alterations in cardiac structure and function in individuals with ESRD. Additionally, IMA was discovered to be a predictor of death in ESRD patients. Our study revealed that the mean of the lipid profile parameters (LDL, HDL, Triglycerides, Total cholesterol) were all higher than normal in both groups. But there was no discernible difference between the two groups. Table (2). The higher parameters of lipid profile in both groups can be explained by the fact that patients undergoing maintained hemodialysis often exhibit abnormalities in lipid metabolism, such as hypertriglyceridemia, elevated lipoprotein-a, and low HDL-c. These abnormalities may donate to the development of atherosclerosis and CVD, ultimately leading to increased morbidity and mortality in these patients [18]. Regarding the correlation between IMA with the other parameters in current study. There was a positive correlation with BMI (p= 0.011). The same result was presented by PIVA et al. [7] study, a significant correlation between IMA and BMI was found ($P < 0.001$) Table (3) & figure 4, figure 5, figure 6. Being obese is a long-term condition that has several links to the generation of free radicals. Some potential causes of the oxidative stress in obesity include hyperglycemia, elevated muscular activity, insufficient antioxidant defences, lipid oxidizability, persistent low-grade inflammation, hypertension, and hyperleptinemia. All of these factors increase the ability to atrial stiffness occurrence [19].

Serum IMA levels was positively correlated with patients' total cholesterol (r=0.208 and p=0.049), but there was no correlation with (LDL, HDL, or triglyceride) Table (3) & figure 4. This might be explained by the fact that hypercholesterolemia decreases albumin's ability to bind cobalt, which raises IMA, and is linked to an increase in oxidative stress and inflammatory indicators. Oxidative stress appears to be linked to the production of IMA [20]. Similarly, to our result, Han et al. [21] study who observed serum IMA levels correlated with patient's total cholesterol (P<0.05) but not correlated with HDL-C levels. In disagreement with our study, the Ozkurt et al. [22] and Bilgi et al. [23] studies showed no correlation between IMA and TC or LDL. But according to Kotani et al. [24] study, there was a correlation between LDL and IMA. Atherosclerosis in ESRD patients is primarily caused by oxidative stress and the systemic inflammatory process. Changes in IMA levels and a rise in CIMT levels can be seen during this process [25]. According to our research, individuals with ESRD and elevated CIMT typically had greater levels of IMA than those with normal CIMT. We observed a highly positive correlation between IMA with CIMT (p= 0.0001). Thus, we hypothesised that IMA may be utilised as a marker for assessing the progression of atherosclerosis in ESRD patients. Also there is border line statistical significance correlation between IMA and LDL cholesterol (P=0.052). Compared to healthy persons, ESRD patients starting HD have greater pre- and post-dialysis IMA levels [26]. But, there was no correlation between IMA levels and age, parathormone, hemoglobin, CRP, and creatinine. Table (3). This might be as a result of the absence of a history of parathyroidectomy or a drug analysis in our study. According to the Park et al. [27] study, there was a link between IMA and ESR but not between IMA and age. Güçlü et al. [28] study had different correlation between IMA and other parameters. There was a correlation between IMA and ALP (P<0.05), CRP (P=0.007), and parathormone (P=0.010). In current study, the independent factor affecting the level of IMA was BMI, cholesterol and CIMT in hemodialysis patients with p value (0.048, 0.019, 0.001) respectively. Table (4). While in study by Jiao et al. [10], the independent factors affecting the level of IMA was brachial ankle pulse wave velocity which is predictor of arterial stiffness in hemodialysis patients ($P < 0.001$). Other factors such as BMI, SBP, LDL-C, uric acid, glucose, albumin, and creatinine did not have significant association. While Ozkurt et al. [22] study, eGFR was determined by linear regression analysis to be the most significant factor on IMA with ($P <0.001$). In our study, ROC curve analysis presented the best cutoff point for IMA to differentiate between cases and controls was >230 with a sensitivity of 60%, a specificity of 90%, and an AUC of 77.1 %. Table (5). The result of Piwowar et al. [29] study, was that IMA had acceptable sensitivities and specificities. In their study, Sharma et al. [9] examined the predictive power of IMA in ESRD and discovered that an IMA level of 95 KU/L or above had a 76% sensitivity and 74% specificity in predicting death. Additionally, the Jiao et al. [10] research offered 77.4% sensitivity and 86.6% specificity for predicting arterial stiffness, with a threshold value of 90.4 KU/L. For HD patients, cardiovascular illness brought on by accelerated atherosclerosis is the main cause of morbidity and death. A higher CIMT is thought to be an early indicator of atherosclerosis. Cardiovascular illness that affects distant vascular beds, including the brain, peripheral, and coronary artery vascular beds, is linked to CIMT [30].

Table 1: Demographic data of the studied groups

		Group A (Normal CIMT)	Group B (increased CIMT)	Test value	P-value	Sig.
Age (years)	Mean ± SD	50.45 ± 13.34	50.90 ± 14.21	-0.148•	0.883	NS
Sex	Female	24 (40.0%)	15 (50.0%)	0.814*	0.367	NS
	Male	36 (60.0%)	15 (50.0%)			
Dialysis vintage (months)	Median (IQR)	48 (36 –96)	54 (24 – 96)	-0.439‡	0.661	NS
HCV infection	Negative	31 (51.7%)	10 (33.3%)	2.710*	0.100	NS
	Positive	29 (48.3%)	20 (66.7%)			
Hypertension	No	22 (36.7%)	9 (30.0%)	0.394*	0.530	NS
	Yes	38 (63.3%)	21 (70.0%)			
Weight(kg)	Mean ± SD	77.84 ± 7.97	82.97 ± 6.44	-3.052•	0.003	HS
BMI (kg/m^2)	Mean ± SD	27.60 ± 2.85	29.37 ± 2.78	-2.810•	0.006	HS

Nonsignificant (NS); Significant (S); highly significant (HS)
*: Chi-square test •: Independent t-test; ‡: Mann Whitney test

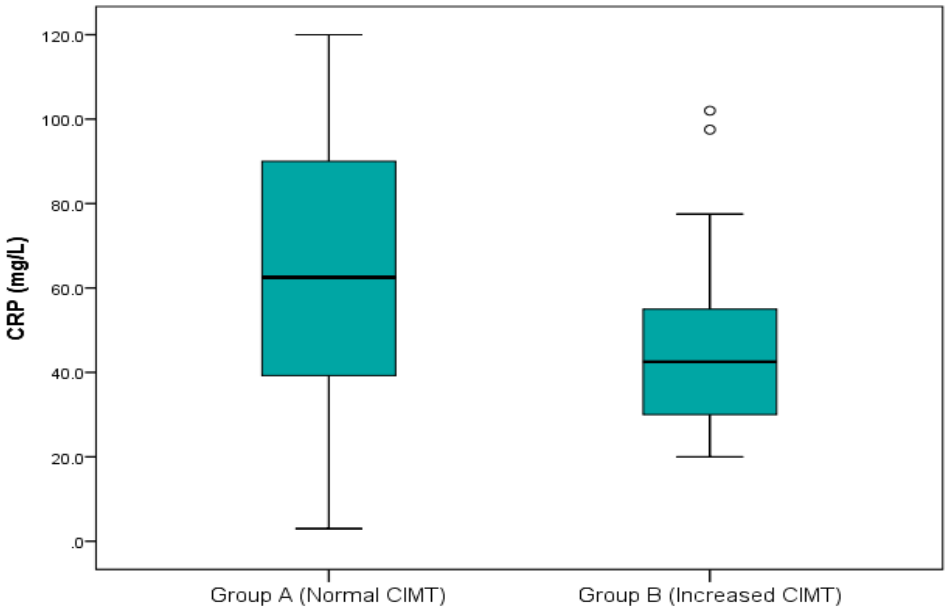

Figure 1: Comparison between CIMT and CRP.

Table 2: Laboratory data of the studied groups

		Group A (Normal CIMT)	Group B (increased CIMT)	Test value	P-value
Cr (mg/dL)	Mean ± SD	7.89 ± 2.66	6.88 ± 2.75	1.687•	0.095
URR	Mean ± SD	69.51 ± 12.69	68.95 ± 9.13	0.215•	0.831
Ca (mg/dL)	Mean ± SD	8.01 ± 0.88	8.16 ± 1.17	-0.671•	0.504
PO4 (mg/ml)	Mean ± SD	5.14 ± 1.34	4.59 ± 1.14	1.907•	0.060
PTH (pg/ml)	Median (IQR)	251.5 (169.5 – 384)	198 (170 – 520)	-0.317‡	0.751
Hb (g/dL)	Mean ± SD	9.37 ± 1.82	9.01 ± 1.49	0.940•	0.350
Albumin (g/dL)	Mean ± SD	3.93 ± 0.33	3.93 ± 0.37	-0.043•	0.966
LDL cholesterol (mg/dL)	Mean ± SD	145.75 ± 26.62	152.33 ± 21.90	-1.170•	0.245
HDL cholesterol (mg/dL)	Mean ± SD	33.23 ± 5.60	35.47 ± 5.61	-1.783•	0.078
Triglycride (mg/dL)	Mean ± SD	132.05 ± 20.03	128.47 ± 18.88	0.815•	0.417
Total Cholesterol (mg/dL)	Mean ± SD	205.08 ± 25.32	213.30 ± 24.33	-1.470•	0.145
CRP (mg/L)	Median (IQR)	55 (33.25 – 82.5)	42.5 (30 – 55)	-1.760‡	0.078
IMA (ng/ml)	**Median (IQR)**	**120 (90 – 180)**	**270 (110 – 300)**	**-4.185‡**	**0.000**

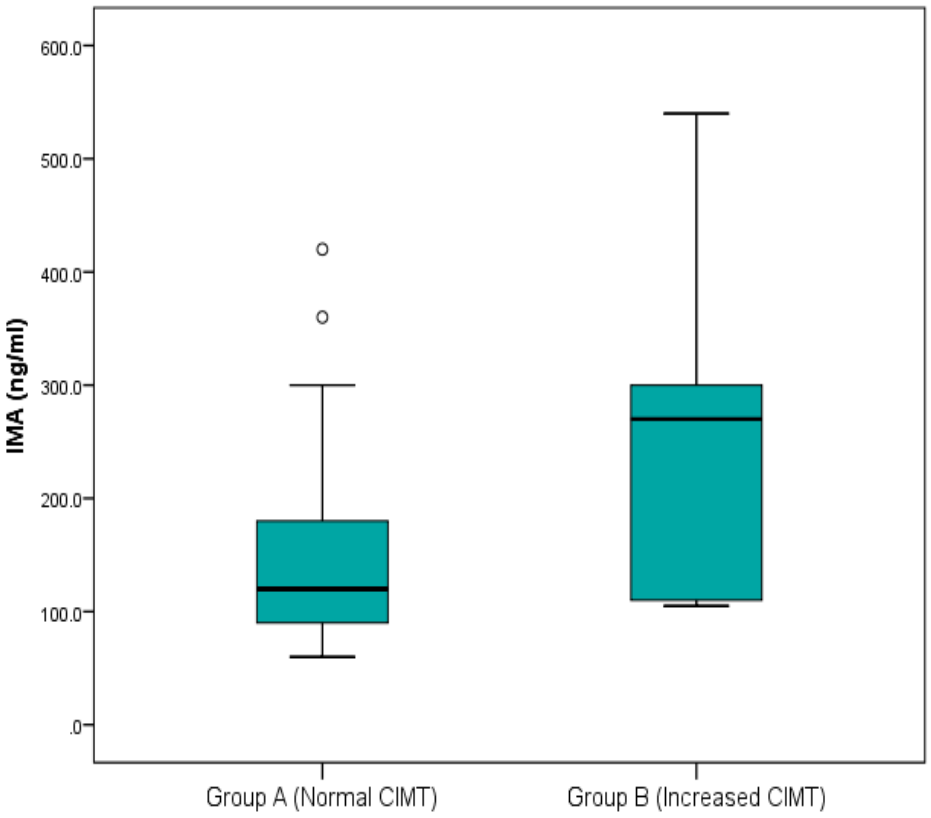

Figure 2: Comparison between the studied groups and IMA**.**

Table 3: Correlation between IMA with the other parameters in all patient groups (No of patients =90).

	IMA	
	r	**P-value**
Age(years)	-0.127	0.233
Dialysis vintage (months)	0.083	0.435
Weight(kg)	0.088	0.407
BMI(kg/m²)	**0.268***	**0.011**
Cr (mg/dL)	-0.119	0.266
URR	0.001	0.992
Ca (mg/dL)	-0.008	0.942
PO4 (mg/ml)	-0.023	0.833
PTH (pg/ml)	-0.138	0.195
HB (g/dL)	-0.113	0.290
Albumin (g/dL)	-0.017	0.872
LDL (mg/dL)	0.205	0.052
HDL (mg/dL)	0.041	0.699
Triglycride (mg/dL)	0.071	0.504
Total Cholesterol (mg/dL)	**0.208***	**0.049**
CRP (mg/L)	-0.031	0.772
CIMT (mm)	**0.376****	**0.000**

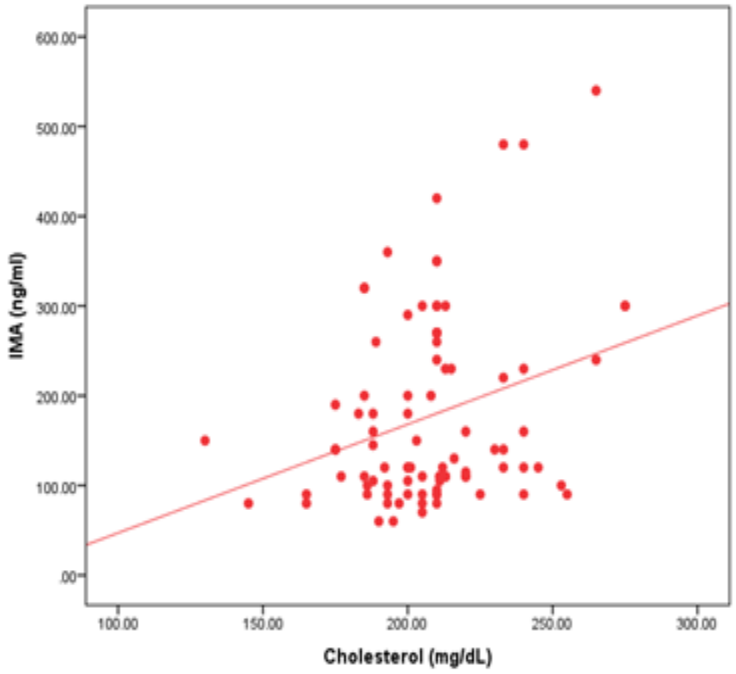

Figure 3: Correlation between total cholesterol and IMA.

Table 4: Multivariate linear regression analysis using the backward method for parameters affecting the level of IMA in all patient groups.

	Un standardized Coefficients		Standardized Coefficients	T	P-value
	B	**SE**	**Beta**		
BMI	**6.652**	**3.456**	**0.186**	**1.925**	**0.048**
Cholesterol (mg/dL)	**0.944**	**0.394**	**0.227**	**2.397**	**0.019**
CIMT (mm)	**414.298**	**123.917**	**0.323**	**3.343**	**0.001**

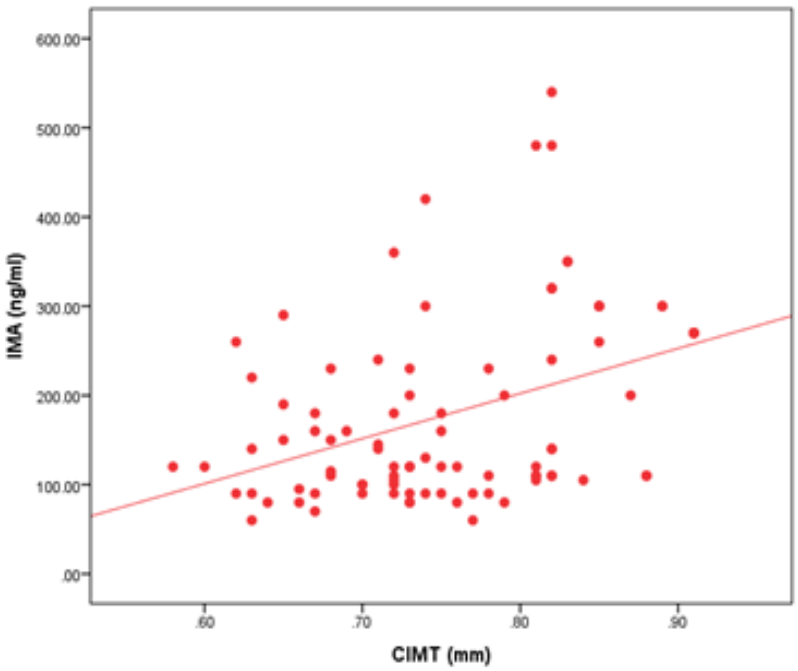

Figure 4: Correlation between CIMT and IMA.

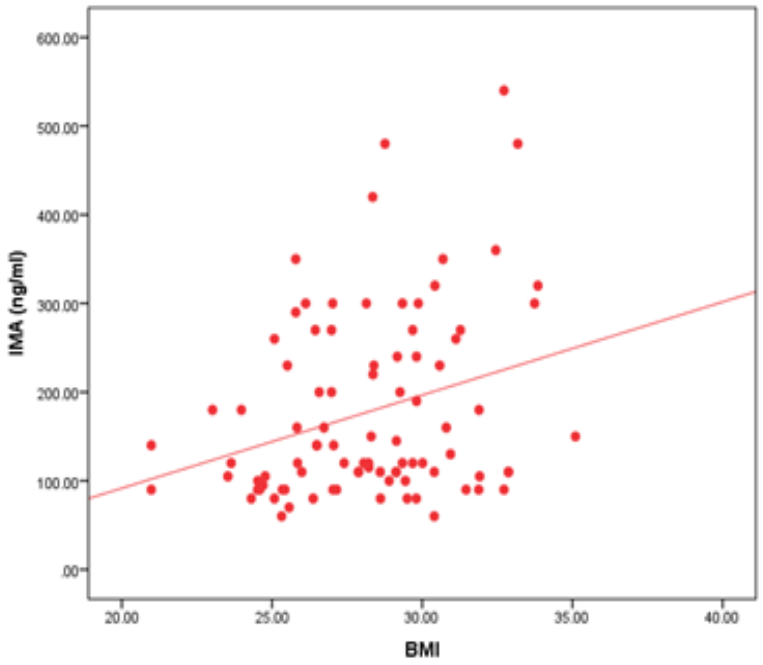

Figure 5: Correlation between BMI and IMA.

Table 5: Receiver operating characteristic curve (ROC) between studied groups regarding IMA.

Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
IMA (ng/ml)	**0.771**	**>230**	**60.0**	**90.0**	**75.0**	**81.8**

AUC: area under curve

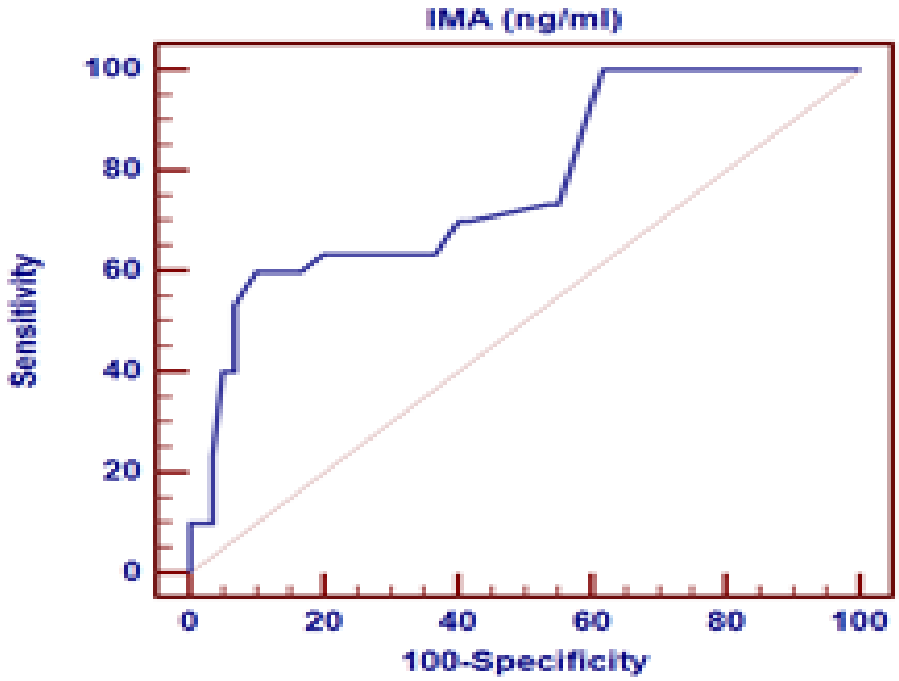

Figure 6: ROC curve between group A and Group B regarding IMA

Table 6: Correlation between CIMT and other parameters in all patient groups (No of patients =90).

	CIMT (mm)	
	R	**P-value**
Age (years)	0.003	0.977
Dialysis vintage (months)	-0.112	0.291
Weight (kg)	**0.294****	**0.005**
BMI (kg/m²)	**0.265***	**0.011**
Cr (mg/dL)	**-0.235***	**0.026**
URR	0.048	0.656
Ca (mg/dL)	0.063	0.555
PO4 (mg/ml)	-0.099	0.351
PTH (pg/ml)	-0.038	0.723
HB (g/dL)	-0.087	0.415
Albumin (g/dL)	-0.016	0.883
LDL (mg/dL)	0.081	0.448
HDL (mg/dL)	0.148	0.163
Triglyceride (mg/dL)	-0.033	0.756
Total Cholesterol (mg/dL)	0.119	0.266
CRP (mg/L)	-0.052	0.627
IMA (ng/ml)	**0.376****	**0.000**

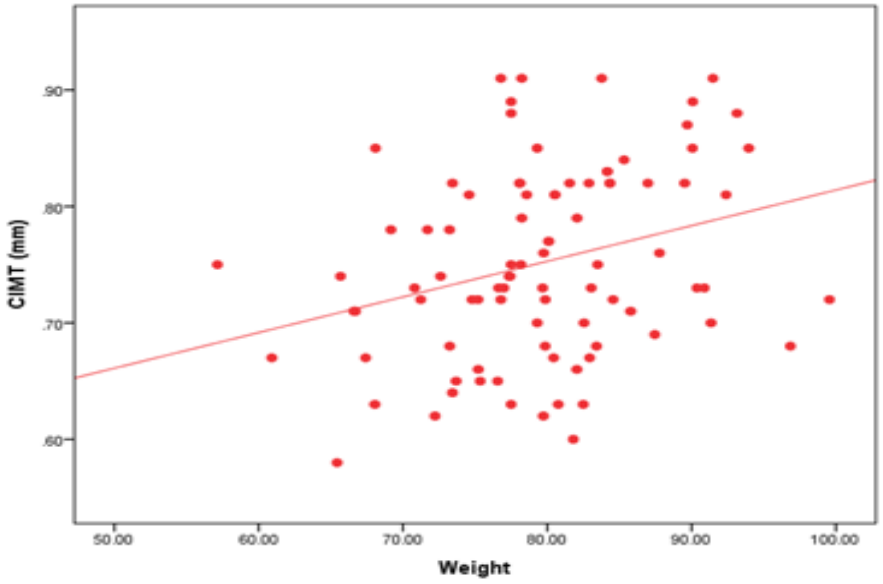

Figure 7: Correlation between weight and CIMT.

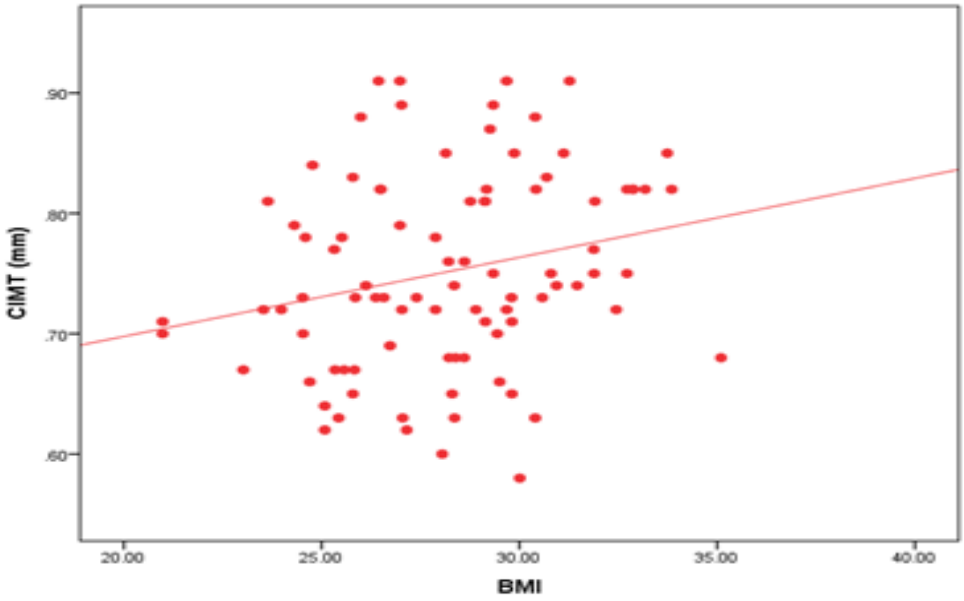

Figure 8: Correlation between BMI and CIMT.

Table 7: Multivariate liner regression analysis for predictors of CIMT in all patient groups.

	Un standardized Coefficients		Standardized Coefficients	t	P-value
	B	SE	Beta		
Weight	**0.003**	**0.001**	**0.261**	**2.834**	**0.006**
BMI	**0.004**	**0.003**	**0.134**	**1.403**	**0.164**
IMA (ng/ml)	**0.000**	**0.000**	**0.322**	**3.357**	**0.001**
Cr (mg/dL)	**-0.008**	**0.003**	**-0.250**	**-2.741**	**0.007**

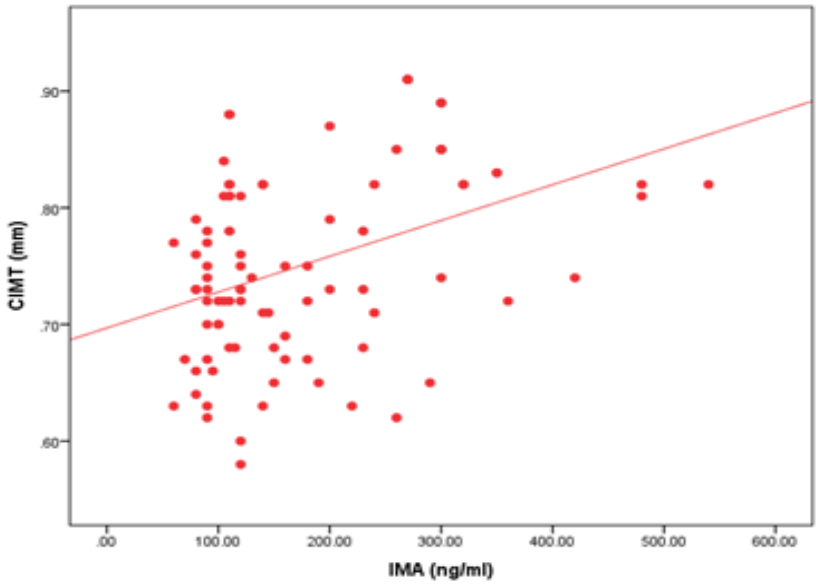

Figure 9: Correlation between IMA and CIMT.

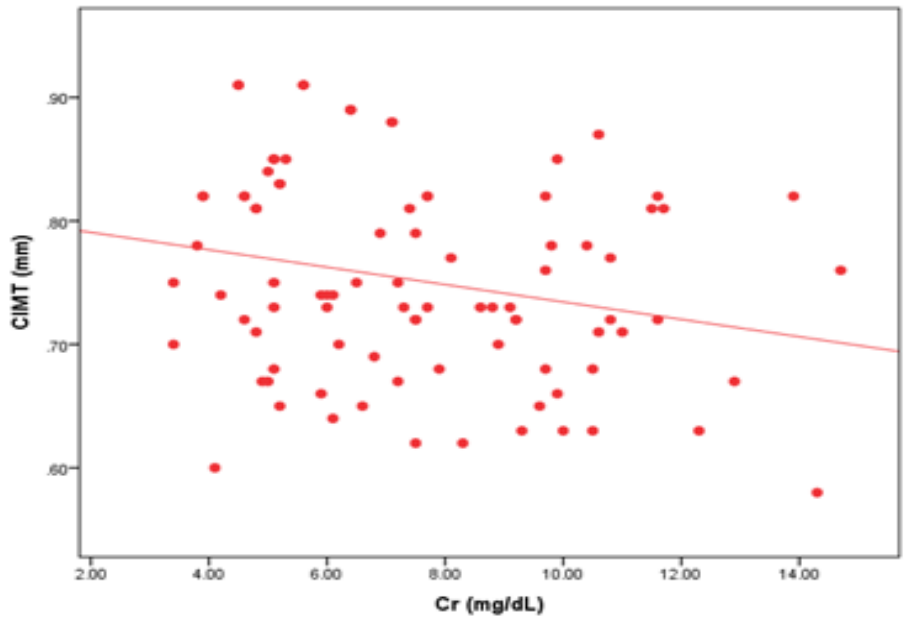

Figure 10: Inverse correlation between Creatinine and CIMT.

The current study revealed that CIMT had correlation with weight and BMI Table 6 & figure 7, figure 8, figure 9. This was documented previously by Asicioglu et al. [31] who reported, in univariate and multivariate analysis that weight was correlated with CIMT (Figure 10). They recommended use of weight as a simple and reliable method of evaluating risk of atherosclerosis. Moreover, the association of weight with CVDs was well recognized by them. Postorino et al. [32] also considered weight as an independent predictor for cardiovascular mortality in predialysis CKD patients and ESRD patients. In our study, no association between CIMT and any other conventional or unconventional cardiovascular risk factor was discovered. As we revealed no correlation between lipid profile and CIMT. Table (6). This coincides with the finding of Tarantino et al. [33] who reported that serum lipoprotein concentration was not associated with CIMT or with early atherosclerosis. This may be attributable to the fact that, in their studies, most of their cases were on statin medication; consequently, the influence of these factors on CIMT data cannot be excluded. The Tsimihodimos et al. [34] research

showed that lipid-lowering drug usage in CKD patients had a limited impact. However, a minority of those receiving these drugs achieved significant improvement in cardiovascular morbidity and mortality independently of the baseline lipid values. Yildiz et al. [35] study had different results, as there was a correlation between CIMT and age, creatinine, albumin, CRP and PTH. In Kuswardhani et al. [36] study, CIMT was correlated with age, albumin, phosphate, and CRP. Nassiri et al. [37] study, it examined how hemodialysis patients' mean and maximal carotid intima-media thickness varied according to CVD risk variables and found among all the studied variables, age, CRP, mean arterial blood pressure and DM had correlations with the mean CIMT. The independent parameters in this study that affected the CIMT level were weight (P<0.006), IMA (P<0.001), and creatinine (P<0.007). Table (7). While in Kuswardhani et al. [36] study, age only was the independent factor affecting the level of CIMT (P<0.001).

5. Conclusion

IMA is a predictive marker of increasing CIMT as well arterial stiffness in hemodialysis patients. The most independent factors affecting IMA were CIMT, cholesterol and BMI. The cutoff value of IMA is >230ng/ml which might be used to differentiate between individuals with normal CIMT and individuals with increased CIMT implying the process of atherosclerosis.

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