Carotid Intima-media Thickness in Hemodialysis Patients and Related Biochemical and Clinical Factors

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Introduction. Cardiovascular complications are the most frequent cause of death in chronic kidney disease that happens due to both general and uremic risk factors. Recently, the medical literature has declared the carotid artery intima-media thickness to be an indicator for predicting cardiovascular diseases.

Methods. This paper is an attempt to introduce an analytical cross-sectional study of 128 hemodialysis patients. The researchers collected the data by reviewing medical records, interviewing the patients, chemical analysis of the patient's serum and carotid artery Doppler ultrasound, and providing the relevant questionnaire. We performed descriptive statistics, bivariate correlation, and general linear model (GLM) analysis. And, the significance level of hypothesis tests was .05.

Results. Seventy-three patients (57%) were male, and 55 (43%) were female. The mean and standard deviation of the age was 58.66 ± 15.54 years. Nearly 42% of patients affected by diabetes, 95.3% were hypertensive and 28.1% had a history of cardiovascular disease. In the bivariate analysis, age, serum albumin, serum magnesium, hypertension, and history of cardiovascular disease showed a statistically significant relationship with carotid intima-media thickness (CIMT). In GLM, we observed a statistically significant relationship between CIMT, age and magnesium.

Conclusion. Increased CIMT is observed in a considerable percentage of hemodialysis patients. Age and serum magnesium concentration demonstrate a statistically significant association with CIMT. We recommend more precise long-term longitudinal follow-up studies to investigate the relationship between biochemical risk factors and CIMT. Therefore, multivariate analysis is necessary to assess the simultaneous effects of independent variables and manage influences of confounding factors. We also recommend developing a practical guideline for periodic determination of CIMT in hemodialysis patients to implement convenient preventive or therapeutic measures.

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INTRODUCTION

Chronic kidney disease (CKD) is one of the substantial health problems, the incidence and the prevalence of which are increasing globally.[1] Patients with end-stage kidney disease (ESKD) need hemodialysis and may experience many complications and comorbidities. They have a higher mortality rate than the general population.[2]

Cardiovascular diseases are the most frequent causes of mortality and morbidity in hemodialysis patients.[3] The mortality rate in ESKD patients due to cardiovascular diseases is about 15 times higher than the general population.[4] In practice, cardiovascular disease and chronic kidney disease possess common risk factors and contribute to complications and consequences. In addition, CKD is considered an independent risk factor for cardiovascular disease.[5]

In recent decades, researchers have conducted numerous studies concerning carotid intima-media thickness (CIMT). They have also investigated the mechanism of this complex process and its contributing risk factors, like age, sex, genetic background, smoking, hypertension, diabetes, serum cholesterol, and obesity.[6,7] According to the findings of several studies, CIMT can serve as a predictor of the progression of generalized atherosclerosis throughout the body.[8] By determining CIMT, we can fairly appraise the intensity of medial calcification of large arteries.[9] CIMT is linked to an increase in the incidence of cardiovascular and cerebrovascular diseases [10] and predicts cardiovascular events, independent of other known risk factors like age.[11]

Atherosclerosis and arteriosclerosis are more prevalent in hemodialysis patients than in the general population.[12,13] Similarly, the average size of CIMT is considerably larger in these patients,[14] therefore, it can serve as an overall indicator of the changes caused by various risk factors over time.[15]

Currently, medical literature has considered the significance of variables influencing CIMT in hemodialysis patients.[16-19] In these patients, both traditional cardiovascular risk factors and uremia, as an independent risk factor, contribute to the development of atherosclerosis and increased CIMT size.[20] Additionally, chronic inflammation and malnutrition (hypoalbuminemia) play important roles in the development and progression of atherosclerosis.[21] More recently, large-scale studies have been conducted on serum magnesium concentration in non-dialysis and dialysis patients. Magnesium is one of the most abundant cations in the body; its deficiency contributes to hypertension and increases the risk of all-cause and cardiovascular mortality in CKD and non-CKD patients.[22-25] It also prevents vascular calcification by inhibiting the action of phosphate in the apoptosis of smooth muscle cells.[26] In this study, we investigated the CIMT in chronic hemodialysis patients and its relationship with various factors.

MATERIALS AND METHODS

One hundred and twenty-eight hemodialysis patients, for at least three months, referred to the dialysis departments of the two teaching hospitals affiliated with Lorestan University of Medical Sciences in 2020 were enrolled in this cross-sectional study.

A structured questionnaire was used to collect information on variables including age, sex, place of residence, dialysis center, smoking, duration of dialysis, and history of diabetes mellitus, hypertension, and cardiovascular diseases.

Before initiating the dialysis session, members of the research team collected fasting blood samples from the patients for laboratory biochemical tests. The serum concentrations of calcium, phosphorus, magnesium, parathyroid hormone, vitamin D3, total cholesterol, triglyceride, creatinine, blood urea nitrogen (BUN) and albumin were measured by a specific technician. In addition, the instruments and methods for conducting tests were also the same for all samples.

In the next step, the patients were referred to the radiology center for the measurement of the size of CIMT. After 15 minutes of rest in the waiting room, the patients were placed on the ultrasound bed in a supine position with their heads tilted slightly backward. A single experienced radiologist evaluated the carotid arteries of the patients using a GE Voluson E6 ultrasound machine (GE Healthcare Austria GmbH & Co OG, with a 12 MHZ frequencies linear array transducer). The techniques and the equipment were the same for all patients. The radiologist measured the size of CIMT in millimeters on both sides of the neck in three areas with no arterial plaques (1.5 cm distal to the common carotid artery, carotid bifurcation area, and proximal internal carotid artery). The average size of CIMT for each side was calculated, and the larger one was considered the basis for statistical analysis.

We employed the bivariate correlation test to demonstrate the relationship between two continuous quantitative variables. For comparing the means of CIMT in diverse groups of binary categorical variables, independent samples t-tests, and for variables with more than two categories, analysis of variance (ANOVA) was used. To calculate the simultaneous effect of independent continuous quantitative and categorical variables on CIMT, the univariate general linear model (GLM) was applied. In this model, we considered the interaction between variables as well. SPSS software version 20 was used for data analysis with a significance level of .05. The results are shown in tables and graphs.

RESULTS

This study included 128 patients undergoing hemodialysis for at least three months, 73 males (57%) and 55 females (43%). We specified the size of CIMT and assessed its relationship with biochemical and clinical factors. The mean and standers deviation (SD) for age of patients was 58.66 ± 15.54 years.

Concerning the body mass index, 10.9% of patients were underweight (BMI < 18.5 kg/m^2); 57.8% maintained normal weight (BMI 18.5 to 24.9 kg/m^2); 23.4% were overweight (25.0 to 29.9 kg/m^2); and 7.8% were classified as obese. In addition, 42.2% of the patients were affected by diabetes; 28.1% had a history of heart disease; 95.3% were hypertensive; 3.9% had a history of organ transplantation; 13.3% had a history of smoking.

Descriptive statistics for the size of CIMT in millimeters were 1.21 ± 0.25 (mean ± SD), median 1.3, mode 1.4, minimum 0.6, and maximum 1.6. The median was 1.3, which means half of the patients had a CIMT greater than 1.3 (Table 1).

We observed a positive linear relationship between CIMT and age in bivariate correlation analysis. We also found that serum magnesium and albumin maintained a negative linear relationship with CIMT. Other variables did not demonstrate any significant correlation with CIMT. (Table 1, Figure 1, and Figure 2)

Table 2 shows the results of independent samples t-test for the comparison of mean sizes of CIMT according to different categories of binary variables. We also applied an analysis of variance (ANOVA) to investigate the difference among mean size of CIMT for three or more groups. The independent t-test analysis showed a more considerable CIMT in patients with hypertension or cardiovascular disease. Likewise, CIMT in patients with diabetes was more prominent than in non-diabetics, although it was not statistically significant (Table 2).

One-way ANOVA did not indicate any difference in the average size of CIMT among the three types of hemodialysis vascular access.

Considering the foregoing findings, we modeled the data to investigate the simultaneous effects of the independent variables on CIMT. Since the independent variables consisted of categorical and continuous ones, we implemented a GLM analysis. Table 3 displays the parameter estimation for

Table 1. Descriptive Statistics of the Study Variables and Bivariate Correlation Analysis Between Them and CIMT (n = 128)

Variable	Descriptive Statistics				Correlation Between the Variable and CIMT	
	Minimum	Maximum	Mean	SD	Pearson Correlation Coefficient	*P*
Age, y	14	85	58.66	15.54	0.721	< .001
Duration of Dialysis, mo	3	144	31.80	34.32	0.062	> .05
Calcium, mg/dL	5.9	10.3	8.41	0.87	0.04	> .05
Phosphorus, mg/dL	1.4	10.7	4.79	1.44	-0.147	> .05
Ca x P Product	11.34	88.81	40.15	12.33	-0.127	> .05
Magnesium, mg/dL	0.8	4.32	2.03	0.51	-0.268	< .05
Albumin, g/dL	2.9	4.9	3.90	0.42	-0.201	< .05
PTH, pg/mL	7.1	1900	380.10	325.62	-0.095	> .05
Triglyceride, mg/dL	35	424	110.45	68.68	-0.059	> .05
Cholesterol, mg/dL	61	257	126.87	38.32	0.07	> .05
Hemoglobin, g/dL	4.8	16.8	10.62	2.19	0.081	> .05
Vit D3, ng/mL	3	100	30.95	20.16	0.113	> .05
BMI, kg/m^2	14.07	39.56	23.30	4.68	0.055	> .05
CIMT, mm	0.6	1.6	1.21	0.25	1	-

Abbreviations: CIMT, carotid intima-media thickness; BMI, body mass index; PTH, parathyroid hormone; Ca x P Product, calcium-phosphorus product; SD, standard deviation.

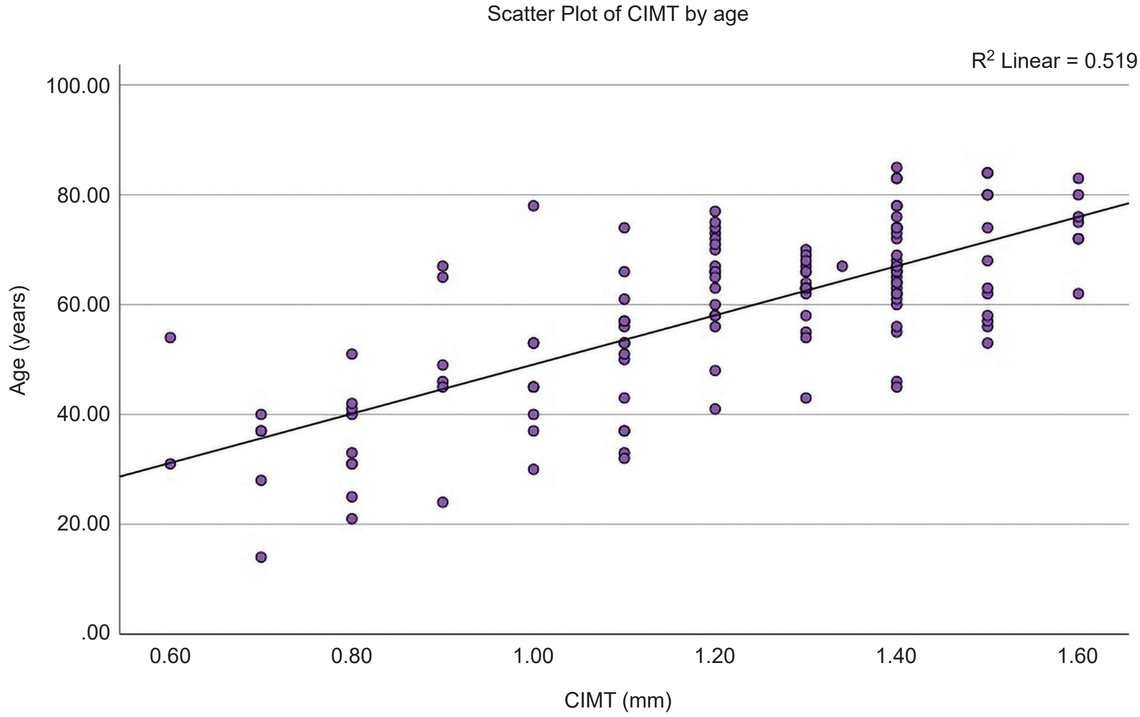

Figure 1. Scatterplot of the Correlation Between Age and CIMT

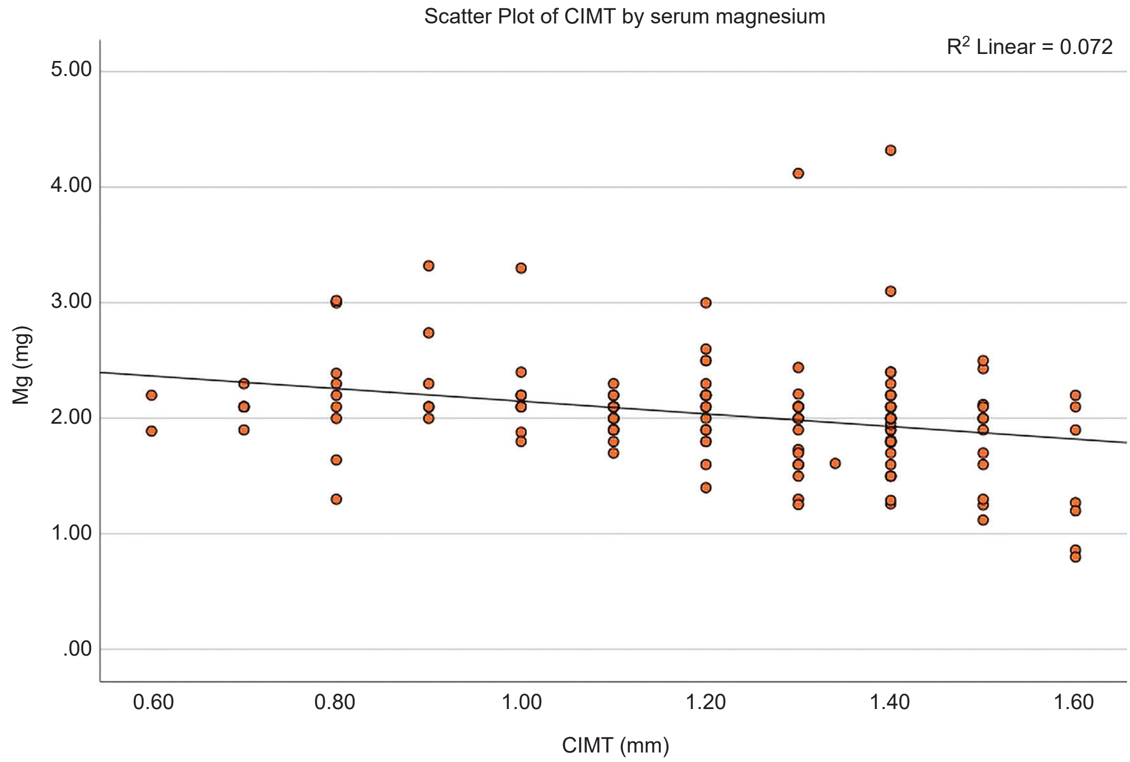

Figure 2. Scatterplot of the Correlation Between Magnesium and CIMT

independent variables using GLM. The GLM model reveals that only magnesium and age variables preserved a statistically significant relationship with CIMT (Table 3).

Additionally, we evaluated the effects of interactions among the independent variables

Table 2. Independent Samples t-test for the Comparison of the Mean Size of CIMT According to the Levels of Binary Variables

Variable	N	Mean	SD	SEM	t	df	*P*
Sex							
Male	73	1.226	0.245	0.028	0.675	126	> .05
female	55	1.194	0.257	0.034			
Smoking Habit							
Yes	17	1.123	0.290	0.070	-1.605	126	> .05
No	111	1.227	0.242	0.022			
Diabetes							
Yes	54	1.261	0.225	0.031	1.884	126	> .05
No	74	1.178	0.262	0.031			
HTN							
Yes	122	1.221	0.243	0.022	2.145	125	< .05
No	5	0.980	0.327	0.146			
Cardiovascular Disease							
Yes	36	1.318	0.193	0.032	3.449	85.026	<.001
No	92	1.173	0.258	0.027			
Transplantation							
Yes	5	1.08	0.259	0.116	-1.221	126	> .05
No	123	1.219	0.249	0.022			

Abbreviations: N, number of patients; SD, standard deviation; SEM, standard error of mean; Df, degrees of freedom.

Table 3. Estimation of Parameters for Independent Variables Using the General Linear Model

Parameter	Coef	SE Coef	T-Value	*P*	95% CI	
					Lower Bound	Upper Bound
Intercept	0.395	0.32	1.23	> .05		
Age	0.0106	0.0012	8.85	<.001	0.008	0.013
Duration of Dialysis	0.0002	0.0005	0.38	> .05	-0.001	0.001
Calcium	0.0045	0.0198	0.23	> .05	-0.035	0.044
Phosphorus	0	0.0123	0	> .05	-0.024	0.024
Magnesium	-0.076	0.0322	-2.36	< .05	-0.14	-0.012
Albumin	0.0007	0.0463	0.02	> .05	-0.091	0.093
PTH	-5E-05	5E-05	-0.93	> .05	0	5.55E-05
Triglyceride	-1E-04	0.0003	-0.49	> .05	-0.001	0
Cholesterol	0.0002	0.0005	0.33	> .05	-0.001	0.001
Hemoglobin	9E-05	0.0084	0.01	> .05	-0.016	0.017
Vit D3	0.0006	0.0008	0.71	> .05	-0.001	0.002
Dialysis Adequacy	0.0537	0.0258	2.08	< .05	0.002	0.105
BMI	0.0022	0.0035	0.62	> .05	-0.005	0.009
Sex						
Male	0.0134	0.0349	0.38	> .05	-0.056	0.083
Female	0*	0	0	0	0	0
Smoking						
Yes	-0.079	0.0491	-1.62	> .05	-0.177	0.018
No	0*	0	0	0	0	0
Diabetes						
Yes	0.0251	0.0364	0.69	> .05	-0.047	0.097
No	0*	0	0	0	0	0
HTN						
Yes	-0.02	0.0889	-0.22	> .05	-0.196	0.157
No	0*	0	0	0	0	0
Cardiovascular Disease						
Yes	0.0064	0.0381	0.17	> .05	-0.069	0.082
No	0*	0	0	0	0	0
Dialysis Access						
AV Fistula	0.1835	0.098	1.87	> .05	-0.011	0.378
Catheter	0.195	0.101	1.93	> .05	-0.006	0.395
Graft	0*	0	0	0	0	0

*This parameter is set to zero because this category of the categorical variable is treated as the reference.

on CIMT and did not observe any statistically significant relationship.

DISCUSSION

This study investigated the relationship between several demographic, biochemical and clinical factors and the size of CIMT in chronic hemodialysis patients.

The median size for CIMT was 1.3 mm in our study, which is larger what is defined in the medical literature as the average size for CIMT in the general population (normally less than one millimeter).[27-29] A high proportion of patients in our study had CIMT of considerable sizes. Other studies have also reported similar results.[30-32]

Typically, CIMT of the carotid arteries increases with age, which is mainly the result of the thickening of the media layer. Several studies have demonstrated a positive linear relationship between age and CIMT in the general population and hemodialysis patients. An age-related systemic process is responsible for the wall thickening of the arteries.[7,33.35] Our study revealed a statistically significant relationship between CIMT and the age of the hemodialysis patients by the bivariate correlation and the GLM analysis.

The increase in CIMT was more prominent in males than in females, in our study, although the difference was not statistically significant. No significant difference was observed in most earlier studies,[36] while some other studies reported a statistically significant increase in CIMT in males compared to females.[37] Different sample sizes and races might be responsible for these diverse results.

In our study, CIMT in patients with diabetes was substantial. However, the relationship was not statistically significant. Some studies revealed a statistically significant relationship between diabetes and CIMT even after adjustment for age and sex.[38,39] In a study of 180 patients, Bulut showed that CIMT in pre-diabetic individuals was greater than those with normal serum glucose level.[40] Kowall *et al.* also reported an association between serum glucose and the size of the CIMT, although this association was not present after adjustment in multivariate analysis.[41] In our study, the size of CIMT was higher in hypertensive patients or those with a history of cardiovascular disease compared to other patients. Nevertheless, GLM multivariate analysis did not verify this relationship. Multivariate analyses of other studies show inconsistent results for the relationship between diabetes or cardiovascular disease and CIMT in hemodialysis patients.[7,38,42,43]

In the general linear model, we did not observe any relationship between serum total cholesterol or triglyceride and CIMT. Some studies reported a significant relationship between cholesterol and CIMT, while others did not.[36,39] Chow *et al.* reported a relationship between race, ethnicity, and CIMT and showed that the increase in serum cholesterol was associated with an increase in CIMT in Indians but a decrease in Australians.[44] However, the multivariate analysis may be partly responsible for the difference in results.

We observed a negative relationship between albumin and CIMT, which was statistically significant, although it was not observed in the multivariate analysis. Other studies have reported inconsistent results. The reports of Kuswardhani *et al.* and Lee *et al.* was similar to the results of our study,[7,45] while Mahmoud *et al.* observed a negative correlation between serum albumin and CIMT, maintained in multivariate analysis.[13]

We did not find any correlation between PTH, vitamin D or calcium and the CIMT in bivariate and multivariate analyses. Likewise, Carnevale *et al.* and Blandon *et al.* did not observe a relationship between serum vitamin D and PTH with the CIMT.[46,47] Studies have reported inconsistent results regarding the relationship between serum calcium level and the CIMT.[7,45]

We noticed a negative relationship between serum phosphorus and CIMT that was not statistically significant. In a hospital-based study, Naveen also reported a negative relationship between serum phosphorus and CIMT.[48] Some studies have reported a positive linear relationship between serum phosphorus and CIMT.[49] Longitudinal follow-up studies with numerous measures of serum calcium and phosphorus concentrations and also the effect of medications that have an impact on serum calcium and phosphorus concentrations are necessary for investigating such relationships.

We also observed that a decrease in serum magnesium concentration is associated with an increase in the size of CIMT. This negative relationship was statistically significant in the bivariate correlation analysis and the multivariate general linear model. Several observational epidemiological and interventional studies have shown the preventive effect of magnesium on vascular calcification.[24,25,50-52] Magnesium binds to phosphorus and prevents the formation of phosphates, thereby inhibits vascular calcification.[26,53,54] It also actively affects calcification factors and prevents smooth muscle cells from differentiating into osteogenic cells. [54] Therefore, the concentration of magnesium in dialysate might affect the size of CIMT in hemodialysis patients.[55]

CONCLUSION

The increase in the size of CIMT is observed in a significant percentage of hemodialysis patients. indicating the increased risk of cardiovascular diseases and necessitates particular attention.

Age and serum magnesium concentration have a statistically significant relationship with CIMT in hemodialysis patients. It is noticeable for the clinicians responsible for hemodialysis patients to monitor their serum magnesium concentration periodically and adjust it appropriately. In addition, repeated examination of CIMT, especially in elderly hemodialysis patients, might support clinicians with timely preventive and therapeutic interventions. For this purpose, conducting longitudinal follow-up studies in hemodialysis patients to carefully scrutinize the relationship between serum biochemicals, particularly magnesium and CIMT, is mandatory.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL CONSIDERATIONS

The ethics committee of Lorestan University of Medical Sciences approved the proposal with code number IR.LUMS.REC.1399.233. We obtained written informed consent from the patients for diagnostic procedures.

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