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ORIGINAL ARTICLE

The Relation between Hemoglobin Level Variability and Carotid Intima-Media Thickness in Chronic Hemodialysis Patients

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ABSTRACT

Background: Hemoglobin variability (HB), defined as hemoglobin value varying between low, normal and high levels, is a common condition among hemodialysis (HD) patients. Atherosclerotic lesions are highly prevalent in patients with chronic kidney disease (CKD). Carotid artery Intima-Media Thickness (CIMT) is noninvasive ultrasound test recommended to screen for heart disease. This work aimed to evaluate the relation between Hemoglobin variability and CIMT among the studied patients. **Methods:** A cross-sectional study was conducted on 70 patients on (HD) attending HD units in Internal Medicine Department in Zagazig University Hospitals and Al- Ahrar teaching hospital during the period from February 2018 to February 2019. Patients underwent history taking, clinical examination, and laboratory investigations. Efficiency of hemodialysis was calculated. CIMT is measured in B-mode ultrasound image using Doppler on carotid arteries. **Results**: A significant positive correlation is detected between hemoglobin change and both CIMT and total cholesterol. However, there is significant negative correlation between hemoglobin change and hematocrit level. A significant negative correlation is present between CIMT and hematocrit value, total protein and CRP. A significant positive correlation is present between CIMT and serum albumin, serum creatinine, BUN and total cholesterol. The best cutoff of hemoglobin variability in prediction of abnormal CIMT is ≥3.45, with sensitivity 86.7%, specificity 90.9%, positive predictive value 72.2%, negative predictive value 96.1% with accuracy 90% ($p<0.001$). **Conclusion:** Hemoglobin variability was associated with high CIMT in chronic HD patients. Hemoglobin variability ≥ 3.45, higher BUN, total cholesterol and CRP increase risk of abnormal CIMT.

Keywords: hemodialysis, hemoglobin, variability

INTRODUCTION

Chronic kidney disease (CKD) is defined by the National Kidney Foundation Kidney Disease and Outcome Quality Initiative (KDOQI) Group to classify any patient who has kidney damage lasting for at least 3 months with or without a decreased GFR or any patient who has a GFR of less than 60 mL/min per 1.73 m2 lasting for 3 months with or without kidney damage (1). The most common manifestation of kidney damage is persistent albuminuria, including microalbuminuria or decreased GFR, with or without evidence of kidney damage (2). Atherosclerotic lesions are highly prevalent in CKD patients (3). Carotid artery Intima-Media Thickness (CIMT) is a noninvasive ultrasound test that is being recommended by the American Heart Association and the American College of Cardiology to screen for heart disease in apparently healthy individuals (4).

CKD, especially in the end stage, is known as an independent predictor of carotid arterial IMT (5).

Hemoglobin variability is the change of hemoglobin level (by >1g/dl) above or below the target range over time (during assessment period). Hemoglobin variability is the extent to which multiple measured hemoglobin values differ from each other within a given time span, whereas the calculated mean of all hemoglobin levels may still remain within the target range. Only 10% of HD patients maintained same hemoglobin level from one month to another (6).

This study aimed at to evaluate the relation between Hemoglobin variability (HB) and CIMt among the studied patients

METHODS

Type, site and time of study

A cross-sectional study was carried out in collaboration between Internal Medicine Department in Zagazig University Hospitals and Al- Ahrar teaching hospital during the period from February 2018 to February 2019.

Criteria of patient selection

Seventy patients with CKD on regular (HD) were included.

Inclusion criteria

Male and female aged ≥18 years old with chronic HD for at least 6 months who had 12-month Hemoglobin data.

Exclusion criteria:

Patients who had hematologic diseases other than renal anemia.

Patient who had malignant diseases.

All patients were subjected to:

Full history taking including:

Demographic and dialysis related data.

Past history for diabetes mellitus was recorded.

Thorough clinical examination.

Laboratory investigations

Laboratory investigations were obtained after hemodialysis session included: creatinine, BUN, liver functions test, CRP, serum sodium, potassium, calcium and phosphorus.

Complete blood count.

Lipid profile: Venous blood sample was taken after at least 12 hours over night fasting.

Calculating efficiency and adequacy of hemodialysis

URR is connected to Kt/V. It is one of the main methods by which dialysis measurement is made. There is the following relationship between the two:

$(K \times t)/V = -\ln(1 - URR)$

Where:

K – dialyzer clearance – blood passage rate in mL/min;

t – duration of dialysis;

V – volume of bodily water.

K/DOQI national guidelines [1] recommend a Kt/V of at least 1.2 for dialysis efficiency.

Measurement of hemoglobin variability:

There are two methods for hemoglobin variability measurement (temporal and non temporal). Temporal method was used here. It if the proportion of time outside certain thresholds, on the basis of either actual hemoglobin measurement or rolling averages of hemoglobin measurements

Imaging technique:

Doppler on carotid arteries: CIMT is measured in B-mode ultrasound image of the carotid tree as a typical double line of the arterial wall. The CIMT measurements were taken at 0.5, 1 and 2 (three different regions) apart from the point of bifurcation of common carotid arteries. The distance between the leading edge of the first echogenic line and the leading edge of the second echogenic line in the posterior wall of the artery was measured at the end of diastolic phase, bilaterally. By obtaining the average of these six measurements in millimeters (mm), mean CIMT was calculated.

Administrative design:

The study protocol was approved from the ethical committee at faculty of medicine, Zagazig university and institutional review board.

All official permissions were obtained from the managers of the Internal Medicine department Zagazig University hospitals and AlAhrar teaching hospital. The objectives of this study were explained to them to ensure their cooperation.

Ethical consideration

Written informed consent was obtained from all participants. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data was collected, coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (**(**IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp**)** software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance difference and association of qualitative variable by Chi square test (X^2). Differences between parametric quantitative independent groups by t test and in non-parametric by Mann Whitney. Multiple parametric by ANOVA followed by LSD, or Kruskal Walis in non-parametric data. P value was set at <0.05 for significant results &≤0.001 for high significant result.

RESULTS

Demographic characteristics of the studied groups:

The mean age of our patients was 48.76 (±9.46) ranged from 31 to 65 years. Males represent 55.7% Mean CIMT was 0.90±0.29 with minimum 0.4 and maximum 1.5 mm. fifteen patients had abnormal CIMT (table 1).

Hemoglobin variability in patients with abnormal CIMT:

There is significant difference between patients with normal and abnormal CIMT concerning hemoglobin variability (table 2)

Correlation between CIMT, hemoglobin change and the studied demographic and laboratory parameters:

There is significant positive correlation between hemoglobin variability and CIMT and total cholesterol. However, there is significant negative correlation between hemoglobin variability and hematocrit level (table 3). There is a significant negative correlation is present between CIMT and all of hematocrit value, total protein and CRP. On the other hand, a significant positive correlation is present between CIMT and serum albumin, serum creatinine, BUN and total cholesterol (table 3).

Performance of hemoglobin variability in prediction of abnormal CIMT:

The best cutoff of hemoglobin variability in prediction of abnormal CIMT among the studied patients is ≥3.45 with area under ROC curve 0.955, with sensitivity 86.7%, specificity 90.9%, positive predictive value 72.2%, negative predictive value 96.1% with accuracy 90% (p<0.001) (table 4, figure 1)

Predictors of abnormal CIMT among the studied patients:

Hemoglobin variability, BUN, Cholesterol and CRP were significant independent predictors of abnormal CIMT. Hemoglobin change ≥ 3.45, higher BUN, total cholesterol and CRP increase risk of abnormal CIMT by 13.75, 4.15, 21.687 and 3.326 folds respectively (table 5)

Table 1. Distribution of the studied patients regarding demographic characteristics and CIMT

Variables	N=70	%
Gender:		
Male	39	55.7
Female	31	44.3
Age:		
Mean ± SD	48.76 ±9.46	
Range	31 - 65	
CIMT:		
Mean ± SD	0.9 ±0.29	
Range	0.4 – 1.5	
Abnormal CIMT	15 (21.4)	
Normal CIMT	55 (78.6)	

Table 2. Comparison between normal and abnormal CIMT regarding hemoglobin variability

	CIMT		
	Abnormal n=15	**Normal =55**	**p**
	Mean ± SD	**Mean ± SD**	
Hemoglobin variability	4.43 ± 0.96	1.91 ± 1.03	<0.001**

Table 3. Correlation between Hemoglobin variability, CIMT and other parameters

	Hemoglobin variability		CIMT	
	r	**p**	**r**	**p**
CIMT	0.686	<0.001**	1	
Hemoglobin change	1		0.686	<0.001***
Age	-0.110	0.363	0.033	0.788
Hematocrit	-0.327	0.006*	-0.353	0.003*
PLTS	0.103	0.396	.067	0.579
TLC	-0.002	0.986	-0.041	0.733
FBS	-0.068	0.480	-0.133	0.272
Hba1c	-0.068	0.578	-0.114	0.349
S.albumin	-0.078	0.523	0.248	0.038*
T.protien	-0.274	0.022	-0.262	0.029*
ALT	0.219	0.068	0.147	0.149
AST	0.000	0.997	0.036	0.764
AL.phosphatase	0.057	0.642	0.036	0.765
S.Creatinine	0.027	0.821	0.260	0.030*
BUN	0.074	0.541	0.365	0.002*
NA	0.043	0.723	-0.072	0.533
K	-0.046	0.703	-0.045	0.709
CA	-0.054	0.659	-0.063	0.607
PH	0.087	0.473	0.134	0.269
Cholesterol	0.673	<0.001**	0.804	<0.001**
TRIGLYCERIDE	-0.069	0.571	0.096	0.427
LDL	-0.021	0.860	-0.009	0.943
PTH	-0.097	0.424	-0.173	0.151
CRP	0.043	0.725	-0.307	0.010*

Table 4. performance of hemoglobin variability in prediction of abnormal CIMT

Area	Cutoff	Sensitivity	Specificity	PPV	NPV	accuracy	P
0.955	≥3.45	86.7	90.9	72.2	96.1	90	<0.001**

**p≤0.001is statistically highly significant PPV: positive predictive value NPV: negative predictive value

Table 5. Multivariate Logistic Regression for Predictors abnormal CIMT among the studied patients

Predictors	P	Odds ratio	95% Confidence Interval	
			Lower	Upper
HB change (>3.45)	0.001**	13.752	5.254	17.542
Serum albumin	0.105	3.012	0.954	9.325
Hematocrit	0.058	2.547	0.874	8.547
Blood urea nitrgen	0.002*	4.150	1.874	19.25
Total Cholesterol	<0.001**	21.687	18.742	25.214
PTH	0.087	2.325	0.987	24.124
CRP	0.021*	3.326	1.578	27.654

OR odds ratio, CI confidence interval
*p<0.05 is statistically significant
**p≤0.001is statistically highly significant

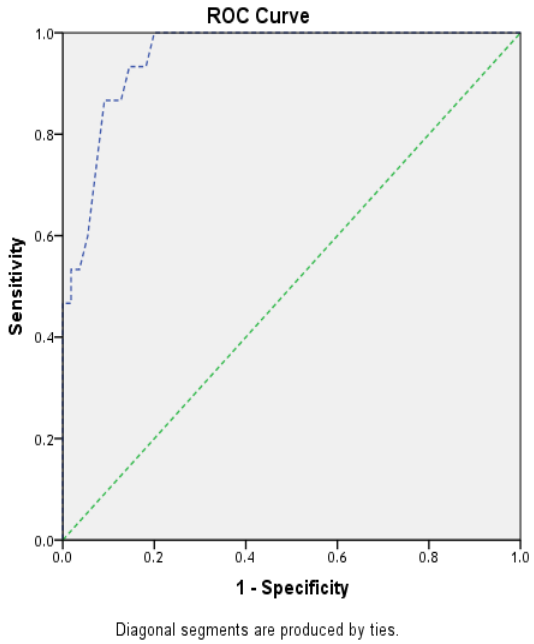

Figure 1. ROC curve showing performance of hemoglobin variability in prediction of abnormal CIMT

DISCUSSION

Hemodialysis patients are highly prone to CVD. CVD accounts for roughly half of mortality among those patients. Atherosclerosis is the most common cause of cardiovascular morbidity in ESRD patients. In healthy middle-aged adults, CIMT values ,between 0.6 and 0.7 mm, have been considered normal, while CIMT of 1 mm or more has been associated with significant increase of CHD risk (7).

CIMT is increased in patients on maintenance HD. Anemia may contribute to endothelial dysfunction by reducing shear stress on the endothelium. Additively, the diminshed nitric oxide (NO) level may accelerate atherosclerosis by increasing LDL oxidation **(8)**. **Shoji et al. (9)** found that CIMT significantly increases in CKD patients.

The mean age of our patients was 48.76 (±9.46). Males represent 55.7%. Mean CIMT was 0.90±0.29 with minimum 0.4 and maximum 1.5 mm.

In healthy Indian adults, the average and maximum CIMT values reported were 0.67 and 0.70 mm, respectively (10).

The measurement of CIMT varies with age. CIMT values >1.0 mm are considered abnormal in younger population and confer increased absolute risk of coronary heart disease (11).

In a study by **Kumar et al. (12)**, 76% of their patients were males versus 75.33% in the control groups. Mean age of CKD was 46.87 ± 14.23 years and that of control group was 47.15 ± 14.12 years.

In our study, there was significant positive correlation between CIMT and hemoglobin variability, BUN, albumin and cholesterol and significant negative correlation between it and CRP. Similar results were reported in other studies **(13-16)**.

CIMT was significantly higher in the patient with CKD at all stages compared to healthy control **(17)**. Other studies detected that CIMT significantly increased with increasing CKD stages **(18-20)**.

Bal et al. (21) found that hemoglobin variability was significantly correlated with age, platelet count, and the number of hospitalizations and inversely correlated with erythropoietin dose per body surface area.

Further studies reported positive correlation between CIMT and other risk factors such as systolic and diastolic blood pressure, LDL and HDL levels, blood urea, serum creatinine, serum calcium, serum phosphorus, and serum uric acid (22-23).

Older age, higher high-sensitivity C-reactive protein, and lower albumin, phosphate, and calcium-phosphate product levels were correlated with higher CIMT. Age was the most important marker for CIMT in subjects on HD (24-25).

In our study, patients with abnormal CIMT had significantly higher variability in hemoglobin, cholesterol and BUN, yet significantly lower CRP and albumin levels. There was a significant association between CIMT and hemoglobin change. Also, hemoglobin change and cholesterol were independent predictors of high CIMT.

Nakashima et al. (26) found that the independent risk factors associated with abnormal CIMT value were age, diabetes mellitus and smoking. **Eckardt et al. (27)** concluded hemoglobin level (<11 g/dl) was associated with an increased mortality risk. Furthermore, a lower body mass index and the timing of hemoglobin values < 11 g/dl were both detected as predictors of mortality of hemoglobin variability. Another study revealed that patients who had a low hemoglobin level (<11 g/dl) for the longest time had the highest mortality risk (28).

Paul et al. (29) concluded that HD is an independent risk factor of atherosclerosis in CRF patients. They also found a significant relationship between CIMT and serum calcium, phosphorus, age and serum cholesterol level. **Marcos et al. (30)** concluded that the CIMT in patients with CKD not requiring HD is associated with coronary calcification, but not to the occurrence of cardiovascular events and death in a 24-month follow-up.

Abbasi et al. (31) found no significant relationships between CIMT and either gender, smoking, serum calcium, phosphate, calcium x

phosphate product, hemoglobin, or uric acid level.

Ganidagli et al. (32) found that hemoglobin variability is associated with an increase in CIMT in HD patients. **Kumar et al. (12)** reported that CIMT and other risk factor like age, gender and DM are independent variables and other risk factors like HTN, alcohol, smokers and dyslipidemia are dependent to each other.

The cross-sectional nature of the study and lack of control group are two main limitations of the current study. Further prospective large scale studies are recommended to evaluate role of hemoglobin variability in prediction of abnormal CIMT and its relation to patient outcome.

CONCLUSION

We revealed in this study that hemoglobin variability was associated with high CIMT in chronic HD patients. Hemoglobin variability ≥ 3.45, higher BUN, total cholesterol and CRP increase risk of abnormal CIMT

Conflict of Interest: Nothing to declare.
Financial Disclosures: Nothing to declare.

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