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Relation Between Serum Ferritin Level and the Left Ventricular Mass Index (LVMI) in Maintenance Hemodialysis Patients

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Abstract: Among hemodialysis (HD) patients, the left ventricular hypertrophy (LVH) is a common cardiovascular morbidity predictor. Ferritin level was considered as a clinical marker of iron storage and associated with cardiovascular mortality in chronic kidney disease (CKD) patients. The relationship between ferritin level and cardiac function in maintenance hemodialysis patients has not yet fully investigated. This study aimed to investigate the relationship between serum ferritin level and left ventricular mass index (LVMi) in hemodialysis patients. In this study, 70 regular chronic hemodialysis patients were included in a cross-sectional study (43 men and 27 women). The patients were sub-grouped into two groups according to the ferritin levels (patients with serum ferritin <800ng/ml (n=40), and patients with serum ferritin ≥800ng/ml (n=30)). Left ventricular mass (LVM), Left ventricular mass index (LVMi) and Left ventricular mass/hight $^{2.7}$ (LVM/Ht$^{2.7}$) were evaluated by echocardiography. The patients with serum ferritin level ≥800 ng/ml showed significantly higher LVM, LVMI and LVM/Ht$^{2.7}$ than other group. LVM, LVMI and LVM/Ht$^{2.7}$ were significantly correlated to ferritin and hs-CRP. Regarding to the linear regression analysis, serum ferritin level was founded to be an independent predictors of LVM/Ht$^{2.7}$ and but not for LVM nor LVMi. While, Highly sensitive C-reactive protein (hs-CRP) was founded to be independent predictors of LVM, LVMi and LVM/Ht$^{2.7}$. This study showed that LVM, LVMI and LVM/ Ht$^{2.7}$ are significantly elevated in patients with serum ferritin level ≥800 ng/ml. The serum ferritin was found to be independent predictors of LVH (represented by LVM/ Ht$^{2.7)}$ in maintenance HD patients.

Keywords: Left Ventricular Mass Index, Ferritin, Hemodialysis, Echocardiography

1. Introduction

Traditional cardiovascular risk factors cannot only explain the high risk for cardiovascular diseases in patients with end-stage renal disease (ESRD) [1]. Non-traditional cardiovascular risk factors, such as malnutrition and chronic inflammation syndrome, abnormal calcium phosphate metabolism, ferritine, hyperhomocysteinaemia and reactive oxygen species induced oxidative stress (OS) become new therapeutic targets in this population [2].

An important independent risk factor of cardiovascular morbidity in patients with CKD is the left ventricular hypertrophy (LVH) which was presented in up to 75% of the patients initiating renal replacement therapy [3].

Diagnosis of LVH using Echocardiographic is depend on

cutoff values based on population studies in which left ventricular (LV) mass was either indexed to body surface area (BSA), height or height raised to the power of 2.7 which represent the algometric growth rate of the heart [4].

Ferritin was considered as an important clinical marker of the state of iron storage and as increased in many chronic inflammatory stages [5, 6]. Ferritin also accelerates the oxidative stress through increasing the formation of reactive oxygen species (ROS) and induces macrophage accumulation [7]. Previous studies have reported that serum ferritin was not only an important risk factor for rapid renal deterioration, but also it seemed to increase morbidity and mortality in chronic kidney disease (CKD) patients and hemodialysis (HD) patients [8, 9]. In more than 30% of hemodialysis patients, inflammation was the possible cause of increased level of serum ferritin. Serum ferritin levels in the range of 200 to 2000 ng/ml may be increased due to a lot of non-iron-related factors including elements of malnutrition-inflammation complex syndrome (MICS) [9].

In a prospective cohort study, ferritin level was independently associated with an increase in cardiovascular mortality risk and could predicts patients' mortality regardless of either inflammatory or nutritional status in patients on dialysis [10]. However, few reports exist on the relationship between serum ferritin level and the LV mass index in regular HD patients. The object of the current study is to examine the association between high serum ferritin level and LV mass parameters in regular HD patients and prove the role high ferritin levels is an indicator of cardiovascular morbidity in HD patients.

2. Methods

2.1. Study Population

A cross sectional study was performed on seventy hemodialysis (HD) patients in Mansoura university hospital, Mansoura, Egypt. All eligible subjects have good adherence and stability to dialysis treatment for at least six months prior to investigation. Vascular access to hemodialysis was performed by means of arterio-venous shunt. A written informed consent was obtained from all patients before enrollment in the study.

Excluded criteria from our study were patients with recent or active infection, patients with malignancy, advanced cardiac diseases (as sever heart failure, severe ischemic heart disease, atrial fibrillation, severe valvular heart lesions), advanced liver disease and the treating with statins and/or non-steroidal anti-inflammatory drugs (NSAIDs) (at least 2weeks before the test).

All patients were received HD three times per week, each session lasted 4 h, and using a polysulfon dialyzer. The dialysis flow rate and the blood flow rate were about 500 ml/min and 200–350 ml/min, respectively.

Demographic data such as age, gender, etiology of ESRD, duration of HD and antihypertensive drugs were recorded from patients' profile.

The studied HD patients were sub-grouped according to the level of serum ferritin into two groups: patients with a serum ferritin level >800 ng/ml and patients with serum ferritin level <800 ng/ml.

2.2. Laboratory Investigations

Blood samples were drawn just before the hemodialysis session for evaluation of hemoglobin (Hb), hematocrit (Hct), iron level, ferritin, and transferrin saturation. Mean values of the three measurements were used to give the high intra-individual variability for ferritin high sensitive C-reactive protein (hs-CRP), Serum albumin level, serum parathyroid hormone (iPTH) and 12 hour fasting lipid profile were also measured.

2.3. Echocardiography

Echocardiography was performed to the patients using a single operator who is blinded to the patients' data and history before the midweek HD session. The measurement of the M-mode echocardiography was performed by the use of an Echocardiography machine (Ultrasound Mindray DC-8 Exp, china) and transthoracic echocardiography was performed in the left decubitus position.

The operator measure the Left ventricular mass (LVM) by using the Devereux formula, corrected by body surface and then expressed as LVM index (LVMi) [11]. Left ventricular hypertrophy was defined as LVMi C134 g/m2 in men and C110 g/m2 in women [12].

2.4. Statistical Analysis

The resulted data was analyzed using Statistical Package for Social Sciences (SPSS) version 16. Qualitative data was presented as number and percent. Chi-Square test was used to comparison between groups. Kolmogrov-Smirnov test was used for normality for quantitative data. Spearman's correlation coefficient was used to test correlation between variables. $P < 0.05$ was considered to be statistically significant $P < 0.001$ was considered to be highly statistically significant.

3. Results

3.1. Baseline Characteristics and Demographic Data of Patients

The demographic data and baseline characters of 70 patients (43 men (61.4%) and 27 women (38.6%)) enrolled in this study were demonstrated in Table 1.

Table 1. *Baseline characteristic and demographic data of both groups of patients.*

Criteria*	Total (n = 70)	Ferritin ≥ 800 ng/ml (n = 30)	Ferritin < 800 ng/ml (n = 40)	P-Value
Age per years	46.92 ± 15.93	48.17±16.25	46.11±15.84	0.585
Gender (Male)	43 (61.4%)	17 (48.8%)	26 (59.0%)	0.362
Weight per kg	74.14 ± 16.13	70.89±13.87	76.18±17.24	0.183
Height per cm	166.85 ± 9.9	164.2±7.76	168.56±11.12	0.075
BMI	27.27 ± 5.5	28.68±5.31	26.43±5.54	0.197
BSA per m²	1.82 ± 0.22	1.77±0.17	1.86±0.25	0.14
WC per cm	99.33 ± 17.53	102.94±16.58	97.12±18.04	0.302
MAC (cm)	30 ± 4.57	30.5±4.72	29.69±4.54	0.584
HD duration per month	43.12 ± 40.86	40.39±33.58	45±45.49	0.632
DM (no/%)	16 (20.3%)	5 (16%)	11 (26.2%)	0.514
HTN (no/%)	57 (72.2%)	20 (64.5%)	37 (80.4%)	0.227
IHD no (%)	13 (17%)	5 (16%)	8 (17.4%)	0.019
HCV no (%)	25 (31.7%)	10 (32%)	15 (32%)	0.922

* BMI: Body Mass Index; BSA: Body surface area; WC: Waist Circumference; MAC: mid Arm Circumference; HD: hemodialysis; DM: diabetes mellitus; HTN: Hypertension; IHD: Ischemic heart disease; HCV: Hepatitis C Virus

Mean age of the patients was 46.92±15.93. They divided into 30 patients with serum Ferritin ≥ 800 ng/ml and 40 patients with serum Ferritin < 800 ng/ml. There are no significant differences between the two groups regarding to baseline characteristic and demographic data of both groups of patients, except IHD, which is more common in patients with serum Ferritin ≥ 800 ng/ml.

3.2. Laboratory Parameters of the Investigated Patients

Highly sensitive C-reactive protein (hs-CRP) as one of signs of inflammatory process was elevated in both groups but it is significantly elevated in patients with very high ferritin level. Serum albumin as one of malnutrition determinants was significantly lower in patients with serum Ferritin ≥800 ng/ml. Parathyroid hormone (PTH) was elevated in both groups but it is significantly elevated in patients with serum Ferritin ≥800 (ng/ml) as shown in Table 2.

Table 2. *Comparative analysis of laboratory parameters between both groups.*

Criteria*	Total (n = 70)	Ferritin ≥800 (ng/ml) (n = 30)	Ferritin <800 (ng/ml) (n = 40)	P-value
Serum Iron	73 (1429)	76 (1230)	68 (1572)	0.481
TSAT (%)	37.97 ± 17.68	39.75 ± 15.08	36.85 ± 19.24	0.491
Alb (gm/dl)	3.69 ± (0.42)	3.58 ± 0.4	3.75 ± 0.44	0.099
ALP*	131.5 (182151)	134 (368167)	128 (40296.7)	0.305
sCa (mg/dl)	8.36 ± 0.9	8.5 ± 0.97	8.28 ± 0.86	0.295
sPb (mg/dl)	4.88 ± 1.58	4.72 ± 1.36	4.98 ± 1.71	0.501
PTH	700.6 ± 59.46	921.09 ± 688.06	566.39 ± 490.7	0.012
Hb (gm/dl)	9.33 ± 1.77	9.1 ± 2.12	9.47 ± 1.5	0.375
WBC*	5.7 (6.09)	6.5 (5)	5.5 (6.8)	0.285
PLT	201.68 ± 65.69	198.46 ± 72.86	203.63 ± 61.69	0.745
HsCRP (mg/L)	4.03 ± 1.49	4.88 ± 1.22	3.24 ± 1.28	0.000
Tc*	135 (2385.68)	132 (3609)	139 (1610.9)	0.668
LDL*	89 (20382)	89 (3368)	93.2 (1139)	0.74
HDL*	25 (101.8)	23.5 (52.2)	28 (131.8)	0.198
Tg	125.1 ± 59.28	132.37 ± 63.6	121.17 ± 57.42	0.441

*TSAT: Transferrin saturation; Alb: Serum Albumin; ALP: Alkaline phosphatase; sCa: Serum Calcium; sPb: Serum Phosphrous; PTH: Parathyroid hormone; HB: Hemoglobin: WBCs: White blood corpuscles; PLT: Platelet count; hsCRP: Highly sensitive C-reactive protein; TC: Totalcholesterol; LDL; Low density lipoprotein; HDL: Highdensity; Tg: Triglycerides

3.3. Echocardiographic Parameters of the Patients

In patients with serum ferritin level ≥ 800 ng/ml, it was shown that LVEDD, LVESD, LVPWd, LVPWs, LVEDV, LVM, LVMI and LVM/$Ht^{2.7}$ were significantly higher than other group (Table 3).

Table 3. *Comparative analysis of echocardiographic parameters between both groups.*

Criteria*	Total (n = 70)	Ferritin ≥800 (ng/mL) (n = 30)	Ferritin <800 (ng/mL) (n = 40)	P-value
LVEDD (cm)	5.33±0.73	5.6±0.56	5.07±0.78	0.004
LVESD (cm)	3.45±0.62	3.62±0.54	3.29±0.66	0.037
IVSd (cm)	1.14±0.15	1.14±0.14	1.13±0.17	0.847

Criteria*	Total (n = 70)	Ferritin ≥800 (ng/mL) (n = 30)	Ferritin <800 (ng/mL) (n = 40)	P-value
IVSs (cm)	1.57±0.21	1.57±0.21	1.57±0.21	0.999
LVPWd (cm)	1.15±0.15	1.19±0.14	1.1±0.16	0.039
LVPWs (cm)	1.68±0.22	1.73±0.18	1.63±0.24	0.066
LVEDV (ml)	159.3±62.35	180.6±53.92	139.38±63.89	0.009
LVESV (ml)	48.43±24.98	54.16±23.73	43.08±25.31	0.086
FS (%)	35.17±5.76	35.16±6.04	35.18±5.6	0.985
EF (%)	70.04±7.31	70.29±7.66	69.81±7.09	0.799
LVM	292.84±80.91	323.23±61.6	263.71±86.97	0.004
LVMI (gm/ m²)	162.73±43.78	183.7±35.17	144.65±42.86	0.001
LVM/$Ht^{2.7}$	74.87(22.57)	79.87(475.6)	69.96±357.3	0.001

*LVEDD: Left ventricular end-diastolic dimension; LVESD: LV end systolic dimension; IVSd: inter-ventricular septum at end- diastole; IVSs: inter-ventricular septum at end-systole; LVPWd: Left ventricular posterior wall thickness at end-diastole; LVPW: Left ventricular posterior wall; LVPWs : Left ventricular posterior wall thickness at end-systole; LVEDV: LV end-diastolic volume; LVESV: LV end systolic volume; FS: fractional shortening; EF: ejection fraction; LVM : Left ventricular mass; LVMI : Left ventricular mass index; LVM/$Ht^{2.7;}$ Left ventricular mass/ hight 2.7

3.4. Correlation Analysis

The Left ventricular mass (LVM) was significantly correlated to ferritin level, hsCRP, hemoglobin and HDL (Table 4). The Left ventricular mass index (LVMI) was significantly correlated to ferritin, hsCRP, hemoglobin, albumin, and total cholesterol. The Left ventricular mass/ $hight^{2.7}$ (LVM/$Ht^{2.7}$) was significantly correlated to ferritin, hsCRP, hemoglobin, albumin and alkaline phosphatase (Table 4).

Table 4. *Correlation between LVM, LVMI and LVM/$Ht^{2.7}$ and Laboratory parameters.*

Criteria*	LVM		LVMI		LVM/$Ht^{2.7}$	
	Rho**	P-value	Rho	P-value	Rho	P-value
sIron	-0.166	0.22	-0.288	-0.038	-0.288	0.031
sFerritin	0.409	0.001	0.511	0.0001	0.57	0.0001
TSAT	-0.146	0.274	-0.113	0.414	-0.208	0.117
hs-CRP	0.404	0.001	0.511	0.0001	0.607	0.0001
Alb	-0.17	0.205	-0.381	0.005	-0.358	0.006
ALP	0.057	0.736	0.267	0.116	0.384	0.019
WBCs	0.044	0.742	-0.122	0.383	0.001	0.994
HB	-0.276	-0.034	-0.295	0.03	-0.276	0.034
PLT	-0.193	0.147	-0.174	0.214	-0.099	0.458
sCa	-0.007	0.958	-0.06	0.664	-0.247	0.064
sPb	0.101	0.459	-0.159	0.256	-0.044	0.749
PTH	0.016	0.904	-0.049	0.726	0.073	0.591
TC	-0.249	0.062	-0.308	0.028	-0.117	0.386
LDL	-0.211	0.115	-0.235	0.097	-0.107	0.43
HDL	-0.355	0.007	-0.243	0.086	-0.221	0.098
Tg	0.029	0.832	-0.113	0.429	0.104	0.441

*sIron: serum Iron; sFerritin: serum Ferritin; TSAT: transferrin saturation; hsCRP: Highly sensitive C-Reactive Protein; Alb: Albumin; ALP: alkaline phosphatase; HB: Hemoglobin; PLT: platelets; sCa: serum Calcium; sPb: serum phosphorus; PTH: parathyroid hormone; TC: Total cholesterol; LDL: low-density lipoproteins; HDL: high-density lipoproteins; Tg: Triglycerides
** rho correlation analysis

3.5. Linear Regression Analysis

Serum ferritin level was found to be independent predictors of LVM/$Ht^{2.7}$ and neither for LVM nor LVMi. The hs-CRP was found to be independent predictors of LVM, LVMi and LVM/$Ht^{2.7}$ (Table 5).

Table 5. *linear regression analysis of variables related to LVM, LVMI and LVM/$Ht^{2.7}$.*

Criteria*	LVM		LVMI		LVM/$Ht^{2.7}$	
	β	P	β	P	β	P
Ferritin	0.214	0.144	0.235	0.086	0.268	0.041
Hs-CRP	0.296	0.047	0.389	0.006	0.403	0.003
Albumin	--	--	-0.112	0.353	-0.098	0.394
Tc	--	--	-0.265	0.024	--	--
HDL	-0.185	.132	--	--	--	--

* hsCRP: Highly sensitive C-Reactive Protein; TC: Total cholesterol; HDL: high-density lipoproteins

4. Discussion

The morbidity and mortality in chronic hemodialysis patients mostly caused by the cardiovascular disease [13]. Left ventricular hypertrophy (LVH) is reported as an independent risk factor of cardiovascular morbidity in CKD patients and affect up to 75% of the patients on renal replacement therapy [3].

Left ventricular mass index (LVMI) was an important predictor of CV events (CVE), but it was not listed among the traditional risk factors in some CV models. In a previous study conducted by Zoccali et al. (2004) found that 1 g/m (2.7)/ month increase in LVMI was associated with a 62% increase in the incident risk of fatal and nonfatal CVE [14].

This study was aimed to identify the association between high ferritin level and LV mass index in HD patients and the correlation between high ferritin levels as an indicator and cardiovascular morbidity in HD patients.

In this study, linear regression analysis among risk factors for increased LVM, LVMi, LVM/$Ht^{2.7}$ and serum ferritin level was found to be independent predictors of LVM/$Ht^{2.7}$ and neither for LVM nor LVMi. The hs-CRP was found to be independent predictors of LVM, LVMi and LVM/$Ht^{2.7}$.

Interestingly, serum ferritin was found to be an independent predictors of LVM/$Ht^{2.7}$.

The importance of LVM/ $Ht^{2.7.}$ over LVM and LVMi was demonstrated previously in studies, which revealed higher prevalence of echocardiographic LVH when detected by LVM/$Ht^{2.7}$ than by LVM indexed to height or to BSA. In a study carried on more than 2000 American populations recruited from 13 US communities with a high prevalence of cardio-metabolic risk factors, the echocardiographic LVH detection by LVM/ $Ht^{2.7}$ led to a higher prevalence (27.6% vs. 10.5%) than that defined by LVM/BSA (i.e. > 116/104 g/m^2). [15]. Moreover, study of Shih-Jen et al. (2012) stated that the highest prevalence of LVH was found when LVM was indexed to $HT^{2.7}$ more than when LVM indexed to height in patients with moderate/severe CKD [16].

Highly sensitive C-reactive protein (hs-CRP) also was found to be an independent predictors of LVM and LVMi and LVM/$Ht^{2.7}$ in HD patients. The same correlation between LVMi and hs-CRP were also reported by previous reports [17, 18]. The correlation of hs-CRP with LVH was a logic correlation as CRP is an acute phase reactant; its level rises dramatically in blood during tissue damage and inflammatory responses [19]. The levels of hs-CRP in regular hemodialysis patients were frequently high due to possible multiple inflammatory conditions such as bacterial or viral infections, vascular access infection, contamination of the blood of the patient with toxins from the dialysis water and persistent micro-inflammatory state from using foreign materials in extra-corporeal circulation [20]. In this study, hs-CRP, as one of signs of inflammatory process, was significantly elevated in patients with very high ferritin level. Moreover, the serum albumin level as one of malnutrition determinants was significantly lower in patients with very high ferritin. The previous study of Kalantar-Zadeh et al. (2004) showed a significant high levels of serum ferritin in chronic hemodialysis patients who had one or both of inflammation and malnourishment and the serum CRP was significantly higher in patients group with serum ferritin > 800 ng/ml [9]. On the contrary, other studies did not find differences in markers of inflammation (hsCRP) in HD patients with normal and high ferritin levels [8, 21, 22]. It has been hypothesized that both elevated and decreased markers of iron status augment the risk for CV disease [23, 24]. The previous results were potentiated the results of the current study that LVH parameters (LVM, LVMI and LVM/$Ht^{2.7}$) are significantly higher in patients with serum ferritin ≥ 800 ng/ml versus other group. However, conflicting results have also been reported in the previous study, which did not observe any association between ferritin or hepcidin concentrations and development of CV events or all-cause mortality in multivariable analyses [25]. This conflict may be explained as the serum ferritin level is affected by several factors other than the amount of iron, including inflammation and tissue damage [26]. Since the inflammation may be the cause an elevated serum ferritin, it is possible that inflammation associated with hyper-ferritinemia can be involved in several complications such as cardiovascular disease including LVH.

This study was considered the potential confounders that the variables related to LVM, LVMI and LVM/$Ht^{2.7}$ were adjusted for linear regression analysis serum ferritin was found to be independent predictors of LVM/$Ht^{2.7}$.

5. Conclusion

In conclusion, LVM, LVMI and LVM/$Ht^{2.7}$ are significantly elevated in patients with serum ferritin level ≥ 800 ng/ml more than that seen in patients with lower levels of serum ferritin. Serum ferritin level was found to be independent predictors of LVM/$Ht^{2.7}$ and not for LVM nor LVMi. hs-CRP is found to be an independent predictors of LVM, LVMi and LVM/$Ht^{2.7}$. Further population-based studies are necessary to establish whether abnormal markers of iron status are associated with the development of CV events in the general population.

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None

Conflict of Interest

All the authors do not have any possible conflicts of interest.

Ethical Approval

The study was reviewed and approved by the ethical committee and Institutional Research Board (IRB) of Mansoura Faculty of Medicine, Mansoura University and the code number is: R/17.03.95.

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