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# RELATION BETWEEN SERUM FERRITIN AND LEFT VENTRICULAR FUNCTIONS IN HEMODIALYSIS PATIENTS

By

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## ABSTRACT

**Background:** Cardiovascular disease is still the most common cause of morbidity and mortality in hemodialysis patients. High serum ferritin is correlated with mortality and cardiovascular outcome in maintenance hemodialysis patients.

**Objective:** To evaluate relationship between serum ferritin level and left ventricular functions and cardiovascular outcomes in hemodialysis patients.

**Patients and methods:** Sixty hemodialysis (HD) patients from Clinic of Internal Medicine Department, Al-Sayed Galal University Hospital, Cairo, Egypt between December 2019 and June 2020. Were enrolled Left ventricular mass (LVM), Left ventricular mass index (LVMi) and Left ventricular mass/height 2.7 (LVM/Ht2.7) were evaluated with transthoracic echocardiography. Patients were classified into two groups according to serum ferritin into 30 patients with serum Ferritin < 800 ng/ml (Group A), and 30 patients with serum Ferritin ≥ 800 ng/ml (Group B).

**Results:** We found statistically significant difference (p-value < 0.05) between studied groups as regard LVESD and LVM/Ht2.7, and statistical significant difference (p-value < 0.001) between studied groups as regard LVEDD and LVMI. The LVEDD, LVMI, LVESD and LVM/Ht2.7 values were significantly higher in group B (High Ferritin) compared with group A (Low ferritin).

**Conclusion:** High serum ferritin level (≥ 800 µg/L) was positively associated with left ventricular hypertrophy in hemodialysis patients.

**Key Words:** Left Ventricular Mass Index, Ferritin, Hemodialysis.

## INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem with a rising prevalence. Low glomerular filtration rate is associated with higher risk for kidney failure requiring dialysis, as well as with cardiovascular disease (CVD), hypertension, anemia, and other metabolic complications *(Abdel-Hady et al., 2013)*. Cardiovascular disease is still the most common cause of morbidity and mortality in hemodialysis patients *(Monfared et al., 2013)*. Left ventricular hypertrophy (LVH) is frequent in maintenance hemodialysis (HD) patients and associated with a poor outcome. The worsening of preexisting LVH is the strongest predictor

of sudden cardiac death in dialysis patients *(Xu et al., 2013)*. Serum ferritin is widely recognized as an acute phase reactant that is nonspecifically enhanced under systemic inflammatory conditions, including chronic kidney disease (CKD), liver disease, and cancer *(Khanna et al., 2017)*. Higher serum ferritin levels can induce macrophage accumulation and increase reactive oxygen species (ROS) formation during inflammation *(Fu et al., 2020)*. It was recently noted that serum ferritin concentration is highly correlated with mortality and cardiovascular outcome in maintenance hemodialysis patients *(Lien et al., 2015)*.

**The goal of our study was to** evaluate the relationship between serum ferritin and left ventricular functions and cardiovascular outcomes in hemodialysis patients.

## PATIENTS AND METHODS

The study was carried out on Internal Medicine Department, Al-Sayed Galal University Hospital, Cairo, Egypt, between December 2019 and June 2020. Sixty hemodialysis (HD) patients were enrolled.

**Inclusion criteria:** Adult patients aged 18 years or more with ESRD on maintenance HD for 3 months or more.

**Exclusion criteria:** Patients with advanced cardiac diseases, Patients who have malignant diseases, Patients with severe hepatic impairment, and patients who were treated with statins and/or non-steroidal anti-inflammatory drugs (NSAIDs) at least two weeks before the test.

All the patients enrolled in the study were subjected to full history and examination and laboratory investigations: (CBC, Serum Ferritin, Serum Iron, TIBC, Tsat, CRP, serum urea and serum creatinine).

**Echocardiographic measurements:**

All patients were examined in detail using standard two-dimensional, pulse-wave Doppler, and M-mode echocardiographic methods. Echocardiographic measurements are performed in the left lateral decubitus position according to the recommendations of the American Echocardiography Society. The study was conducted using an ATL HDI 5000 colored echocardiographic machine (Philips IE 33 Colored Echocardiographic Machine, USA) with TDI software incorporated in the device using 2.5–3.5MHz transducer. The LV ejection fraction (LV-EF) was calculated automatically according to the modified Simpson method using the software on the echocardiography device. Left ventricular (LV) mass was determined using the method described by *(Devereux et al., 1986)*, and the LV mass index (LVMI) was calculated by dividing LV mass by body surface area. LV hypertrophy (LVH) was defined as a LVMI > 131 g/m2 for men and > 100 g/m2 for women. LV systolic function was estimated by the LV ejection fraction (LVEF) using a modified biplane Simpson's method from the apical two-chamber and four-chamber views. Left ventricular dimensions (LVEDD, LVESD) were also measured at the end of both the diastolic and systolic phases.

Data were studied utilizing a Statistical package for the Social Science (SPSS)

version 18.0. Quantitative data were evinced as mean ± standard deviation (M±SD) while qualitative data were evinced as frequency and percentage No(%). Chi-square test: was utilized in comparison of non-parametric data. P-values were established statistically significant at $P < 0.05$.

## RESULTS

No statistical significant difference (p-value > 0.05) was found between studied groups as regard age, sex, Weight and smoking A total of 60 HD patients were included, Patients were classified into two groups according to serum ferritin into 30 patients with serum Ferritin < 800 ng/ml **(Group A)** and 30 patients with serum Ferritin ≥ 800 ng/ml **(Group B)**. The baseline demographic, clinical, and laboratory characteristics was in **Table (1, 2)**.

**Among Group A**, the mean age was 47.6 ± 12.3 years, 19 were males (63.3%). The mean weight was 76.7 ± 15.5 kg/m², 7 patients were smokers (23.3%), 10 patients were diabetic (33.3%), 12 patients were hypertensive (40 %), 4 patients with chronic liver disease (13.3%), and 5 patients with cardiac disease (16.7%). **Among group B,** the mean age was 46.4 ± 10.2 years and 23 were males (76.7 %). The mean weight was 78.6 ± 15.5 kg/m², 11 patients were smokers (36.7%), 15 patients were diabetic (50%), 15 patients were hypertensive (50 %), 3 patients with chronic liver disease (10%), and 6 patients with cardiac disease (20 %) **(Table 1)**.

**Table (1): Description of demographic data in studied groups, Comparison between studied groups as regard co-morbid conditions**

| Parameters \ Groups | | Low group (N = 30) | | High group (N = 30) | | P-value |
|---|---|---|---|---|---|---|
| Age (years) | Mean | 47.6 | | 46.4 | | 0.676 |
| | ±SD | 12.3 | | 10.2 | | |
| Sex | Male | 19 | 63.3% | 23 | 76.7% | 0.260 |
| | Female | 11 | 36.7% | 7 | 23.3% | |
| Weight (kg) | Mean | 76.7 | | 78.6 | | 0.637 |
| | ±SD | 15.5 | | 15.5 | | |
| Smoking | Non | 23 | 76.7% | 19 | 63.3% | 0.260 |
| | Smoker | 7 | 23.3% | 11 | 36.7% | |
| | | Low group (N = 30) | | High group (N = 30) | | P-value |
| HTN | No | 18 | 60% | 15 | 50% | 0.436 |
| | Yes | 12 | 40% | 15 | 50% | |
| DM | No | 20 | 66.7% | 15 | 50% | 0.190 |
| | Yes | 10 | 33.3% | 15 | 50% | |
| Liver disease | No | 26 | 86.7% | 27 | 90% | 0.688 |
| | Yes | 4 | 13.3% | 3 | 10% | |
| Cardiac disease | No | 25 | 83.3% | 24 | 80% | 0.739 |
| | Yes | 5 | 16.7% | 6 | 20% | |

No statistical significant difference between studied groups as regard laboratory data except CRP There are no significant differences between the two groups regarding to baseline characteristic and demographic data of both groups of patients, except CRP, which is higher in group B compared with group A (p-value < 0.05). This means that there were significant positive correlations between serum levels of ferritin and CRP **(Table 2)**.

**Table (2): Comparison between studied groups as regard laboratory data**

| Parameters \ Groups | | Low group (N = 30) | High group (N= 30) | P-value |
|---|---|---|---|---|
| Urea (mg/dl) | Median | 129.5 | 114.5 | 0.117 |
| | IQR | 98.5 – 180 | 105 – 129.8 | |
| Creat (mg/dl) | Median | 9.8 | 8.7 | 0.076 |
| | IQR | 8.2 – 12.3 | 7.3 – 10.3 | |
| Hb (g/dl) | Median | 9.4 | 9.3 | 0.912 |
| | IQR | 8.9 – 10.2 | 8.6 – 10.2 | |
| PLTs (x10³/ul) | Median | 252.5 | 256.5 | 0.982 |
| | IQR | 154.8 – 338 | 148 – 345 | |
| WBCs (x10³/ul) | Median | 7.25 | 7.7 | 0.455 |
| | IQR | 4.6 – 9.9 | 5.8 – 9.6 | |
| CRP (mg/L) | Median | 3.6 | 4.7 | 0.007 |
| | IQR | 3.2 – 4.5 | 3.8 – 6.6 | |
| Calcium (mg/dl) | Median | 8.6 | 8.7 | 0.767 |
| | IQR | 7.7 – 9.6 | 8.2 – 9.5 | |

There were statistically significant differences between studied groups as regard echocardiographic findings We found statistically significant difference (p-value < 0.05) between studied groups as regard LVESD & LVM/Ht2.7, and highly statistical significant difference (p-value < 0.001) between studied groups as regard LVEDD & LVMI. The LVEDD, LVMI, LVESD & LVM/Ht2.7 values were significantly higher in group B compared with group A **(Table 3)**.

**Table(3): Comparison between studied groups as regard echocardiographic findings**

| Parameters \ Groups | | Low group (N = 30) | High group (N = 30) | P-value |
|---|---|---|---|---|
| LVEDD | Median | 5.2 | 6 | **<0.001** |
| | IQR | 4.7 – 5.4 | 5.2 – 6.3 | |
| LVESD | Mean | 3.3 | 3.5 | **0.008** |
| | ±SD | 3.1 – 3.4 | 3.2 – 3.8 | |
| LVMI | Mean | 145.5 | 182.5 | **<0.001** |
| | ±SD | 127.5–167.5 | 165.8– 200.3 | |
| LVM/Ht 2.7 | Mean | 69.5 | 80.5 | **0.01** |
| | ±SD | 59.8 – 81.8 | 70.3 – 88.3 | |
| EF | Mean | 69.8 | 70.3 | 0.190 |
| | ±SD | 69.3 – 70.5 | 69.2 – 71.7 | |

## DISCUSSION

In the current study, we found a statistically significant difference between studied groups as regard LVESD and LVM/Ht2.7, and statistical significant difference between studied groups as regard LVEDD and LVMI. The LVEDD, LVMI, LVESD and LVM/Ht2.7 values were significantly higher in group B compared with group A. LVM, LVMI and LVM/Ht2.7 were significantly correlated to ferritin.

The results of current study were supported by *Eldeeb et al. (2018)* who showed that patients with serum ferritin level ≥800 ng/ml were significantly higher LVM, LVMI and LVM/Ht.

*Fu et al. (2020)* performed a retrospective, observational, cohort study which showed that the underlying cardiovascular mortality was higher among PD patients with serum ferritin values≥100 μg/L than among those with ferritin levels < 100 μg/L. A multivariate Cox regression analysis revealed that an increased serum ferritin level was independently associated with a higher risk of cardiovascular mortality in PD patients after adjusting for relevant confounding factors.

Moreover, *Kuragano et al. (2014)* performed a prospective, observational, multicenter study of 1086 Japanese HD patients and found that hyperferritinemia, defined as serum ferritin > 100 μg/L, is a risk factor for cardiovascular disease, hospitalization and death.

*Son et al. (2019)* retrospectively collected the data of outpatients on maintenance hemodialysis for 5 years. They showed that ferritin levels > 100 ng/mL is associated with increased rates of cardiovascular events.

Our results showed that CRP levels were higher in the high Ferritin group compared with low Ferritin group with statistically significant difference between them.

This results supported by *Elmenyawi et al. (2017)* who reported significant positive correlations between serum levels of ferritin and CRP.

*Abd El-Hafeez et al. (2019)* studied the association between inflammatory markers in hemodialysis patients. They observed statistically significant positive correlation between hs-CRP and serum Ferritin.

## CONCLUSION

High serum ferritin level (≥ 800 μg/L) was positively associated with Left ventricular hypertrophy in maintenance hemodialysis patients.

**Conflict of Interest:**

The authors of the study have no conflict of interest related to this publication.

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# العلاقة بين مستوي الفيريتين في الدم ووظائف البطينى الأيسر في مرضي الاستصفاء الدموي

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**خلفيـــة البحـــث:** تعـــد أمـــراض القلـــب والشـــرايين مـــن أكثـــر المضـــاعفات التـــى يتعـــرض لهـــا مرضـــى القصـــور الكلـــوى المـــزمن والتى تمثل أكثر من 50 ٪ من الوفيات في هؤلاء المرضى.

**الهـدف مـن البحـث:** الهـدف مـن البحـث تقيـيم وظيفـة البطـين الأيسـر فـي مرضـى الاستصـفاء الـدموي عـن طريـق الفحـص بالموجـات فـوق الصـوتية علـى القلـب مـع بيـان العلاقـة بـين مسـتوي الفيـريتين فـي الـدم ووظـائف البطـين الايسـر فـي مرضـي الاستصـفاء الدموي.

**المرضـي وطـرق البحـث:** تـم اجـراء البحـث فـي الفتـرة مـن ديسـمبر 2019 إلـي يونيـو 2020 وشـمل البحـث 60 مريضًـا مـن قسـم الباطنـة بمستشـفي السـيد جـلال الجـامعي، القـاهرة، مصـر, يتعايشـون علـي الاستصـفاء الـدموي, وتـم تقيـيم جميـع المرضـى كـالاتى: أخـذ التـاريخ المرضـى الكامـل والفحـص الاكلينيكـى والتقيـيم المعملـى ويشـمل مسـتوي الفيـريتين بالـدم وتـم عمـل أشـعة بالموجـات فـوق الصـوتية علـى القلـب ثنائيـة الاتجـاه والوضـع و وتـم تقسـيم المرضـي الـي مجمـوعتين حسـب مسـتوي الفيـريتين

بالـــدم: مجموعـــة (أ) شـــملت 30 مريضـــا بمســـتوي فيـــريتين أقـــل مـــن 800 نـــــانوجرام /مـــــل, ومجموعـــــة (ب) شـــــملت 30 مريضـــــا بمستوي فيريتين أكثر من 800 نانوجرام/مل.

**نتـــائج البحـــث:** وجـــود علاقـــة إيجابيـــة ذات دلالـــة إحصـــائية بـــين ارتفـــاع مســـتوي الفيـــريتين بالـــدم وكـــل مـــن حـــدوث تضـــخم البطـــين الأيسروزيادة مستوى بروتين سى التفاعلى.

**الإســـتنتاج:** صـــلاحية مســـتوي الفيـــريتين بالـــدم كعامـــل تنبـــؤ بتضـــخم البطين الأيسر.

**الكلمـــات الدالـــة:** وظـــائف البطـــين الأيســـر، مســـتوى الفيـــرتين فـــى الدم، الغسيل الكلوى.