Int J Pharm Bio Sci 2013 Apr; 4(2): (B) 1017 - 1022

Research Article **BioChemistry**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

ASSOCIATION BETWEEN SERUM FERRITIN AND MARKERS OF MALNUTRITION, INFLAMMATION, ATHEROSCLEROSIS (MIA) IN HEMODIALYSIS PATIENTS

MEERA SHIVASHEKAR*, SHYAM KRISHNAN M AND W EBENEZER WILLIAM

Department of Biochemistry, SRM Medical College Hospital & Research Centre, Chennai, India.

ABSTRACT

Measurements of the Malnutrition, Inflammation and atherosclerosis (MIA) parameters are predictors of the outcome in hemodialysis (HD) patients. Ferritin, used as a marker of iron status, is also a marker of inflammation by its acute phase reaction property. The aim of this study is to find the association between serum ferritin and markers of MIA in HD patients. The study included 42 HD patients, devoid of iron therapy and 26 age and sex matched controls. The biochemical parameters were assessed using autoanalyzer. Results showed that HD patients had higher levels of serum ferritin, transferrin, hsCRP and decreased albumin levels. The study revealed a significant correlation between ferritin and hsCRP and between ferritin and albumin in HD patients. It shows that level of ferritin, an acute phase reactant, is increased in HD patients devoid of iron therapy. This concludes that a strong association exists between serum ferritin and MIA markers in HD patients.

KEYWORDS: **Atherosclerosis, Ferritin, Hemodialysis, Inflammation, Malnutrition.**

MEERA SHIVASHEKAR
Department of Biochemistry, SRM Medical College Hospital & Research Centre, Chennai, India.

INTRODUCTION

Malnutrition, inflammation and atherosclerosis are the common and main cause of morbidity and mortality in hemodialysis patients (HD). Inflammation is responsible for most of the mortality risk factors such as Anaemia, Malnutrition, Vascular disease and left ventricular hypertrophy. A Strong relationship between malnutrition, inflammation and atherosclerosis in an HD patient population suggest the presence of a syndrome called malnutrition, inflammation, atherosclerosis (MIA) syndrome which is associated with an exceptionally high mortality rate. Serum albumin is, to a large extent, influenced by factors other than malnutrition and high concentrations of acute-phase proteins, such as C-reactive protein (CRP), are correlated with low serum albumin in malnourished hemodialysis patients[1,2]. Around 50% of HD patients have elevated serum levels of inflammatory markers which are powerful predictors of mortality after adjustment for other risk factors[3]. Recent data suggests strong linkage between inflammatory markers, endothelial dysfunction and malnutrition in HD patients[6]. In addition, oxidative stress also forms a part of inflammatory mechanism and is associated with oxidative imbalance in which oxidation of different lipids and proteins are predominant which is associated with increased cardiovascular morbidity and mortality[5]. This study was performed at levels of serum ferritin in HD patients devoid of iron therapy with any association between markers of MIA.

SUBJECTS AND METHODS

The study included 42 hemodialysis patients with their medical data & charts attending the Nephrology unit of our hospital. The following exclusion criteria such as smoking, alcohol consumption, vitamin supplementation, antioxidant, acute and chronic infection, hemoglobinopathies and respiratory infections were followed. The inclusion criteria such as HD for at least 1.5 years and devoid of iron therapy were followed. The study was performed in accordance with the approval of the local ethics committee and informed written consent was taken with all patients before they entered the study. Twenty six age and sex matched individuals without any medications were included in this study. Anthropometric and blood pressure measurements were taken for both HD patients and control groups. Blood samples were drawn and collected into appropriate vaccutainer and processed in the laboratory immediately after collection. Laboratory parameters like Serum Ferritin, Albumin, Apo B, Cholesterol, Creatinine, HDL, hsCRP, Transferrin, Triglycerides were analysed using Olympus AU - 400 auto analyser.

STATISTICAL ANALYSIS

All data are expressed as Mean ± SD and statistical analysis was done using the SPSS 20 statistical software (SPSS Inc). The statistically significant mean in control and subject was calculated using t-test. The correlation between Serum ferritin and MIA parameters is estimated by Pearson's correlation analysis. The p values < 0.05 was considered significant.

RESULTS

When compared with controls, hemodialysis patients had higher levels of ferritin, hsCRP and transferrin whereas decreased albumin and HDL levels (Table-2). The correlation study (Table-3) revealed that there is a strong positive correlation existed between ferritin and hsCRP in HD patients. This (Fig–1) shows that both ferritin and hsCRP levels are increased simultaneously in HD patients. Also a significant negative correlation between ferritin and albumin (Fig–2) was observed in HD patients showing a decrease in albumin levels with increase in ferritin. The results thus provide a clear picture that inflammation plays

a major role in HD patients and ferritin is more an acute phase reactant which increases independently of iron therapy.

Table 1
General parameters of both HD patients and controls.

PARAMETERS	HEALTHY CONTROLS (N = 26)	HD PATIENTS (N = 42)
AGE	50.3±7.9	50.3±8.8
BMI (kg/m²)	25±2	20±1*
MALE / FEMALE	14/12	24/18
SYSTOLIC BP (mmHg)	121±13.3	163±11.6*
DIASTOLIC BP (mmHg)	73.8±5.2	69.9±4.4*
WEIGHT (kg)	64.5±5.8	49.7±8.5*
HEAMOGLOBIN (g/dL)	14.5±1	9.7±0.8*

Data expressed (Mean±SD)* P VALUE < 0.05

Table 2
Laboratory parameters in HD patients compared with controls.

PARAMETERS	CONTROL MEAN (N = 26)	PATIENT MEAN (N = 42)
ALBUMIN (g/L)	3.93±0.3	2.88±0.9*
APO B (mg/dl)	87±6	107±8*
CHOLESTEROL (mg/dL)	202±7	178±8*
CREATININE (mg/dL)	0.7±0.2	14.1±5*
FERRITIN (µg/L)	171.2±46.6	335.8±51.3*
HDL – C	45±3	39±5*
hsCRP (mg/L)	1.18±0.63	5.29±1.33*
TRANSFERRIN (mg/dL)	250.6±39.2	319.13±119.5*
UREA (mg/dL)	28.9±6.8	69.8±16.8*

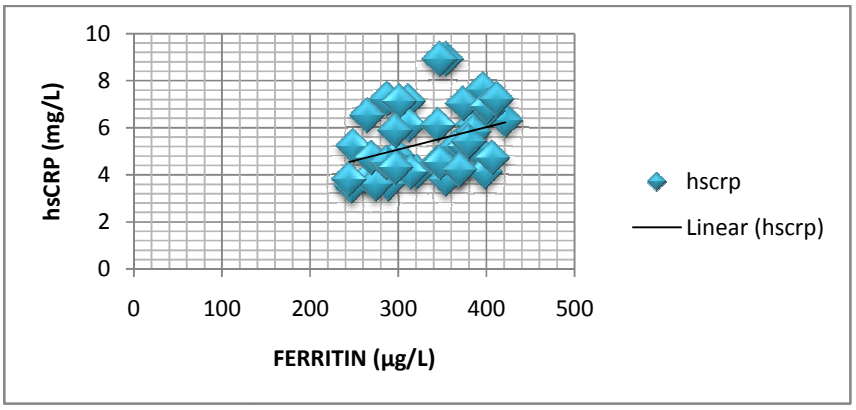
Data expressed (Mean±SD) *P VALUE < 0.05

Table 3
Correlation between Ferritin and Markers of MIA.

PARAMETERS	*r* VALUE	*p* VALUE
FERRITIN & hsCRP	0.826	**0.0001***
FERRITIN & ALBUMIN	-0.747	**0.0001***
FERRITIN & TRANSFERRIN	0.168	0.17 (NS)

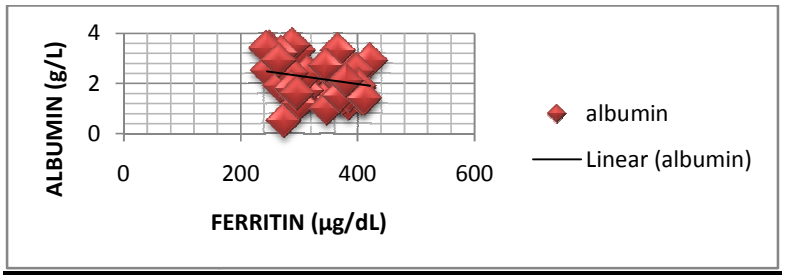
****P VALUE < 0.05 NS – Not significant***

Figure 1
Correlation between ferritin and hsCRP in HD patients.



Ferritin Range : 244.6 – 421.5µg/dL hsCRP Range : 3.4 – 8.9mg/L

Figure 2
Correlation between Ferritin and Albumin in HD patients.



Ferritin Range : 244.6 – 421.5µg/dL Albumin Range : 0.5 – 3.5g/L

DISCUSSION

Malnutrition in HD patients is common and the main cause of morbidity and mortality. Serum albumin, transferrin levels decrease as glomerular filtration rate (GFR) declines, even prior to the start of dialysis. Albumin levels are lower in dialysis patients than among the general population and are a powerful predictor of mortality[8]. Co-morbidity is strongly associated with hypoalbuminemia in the dialysis patient population[13]. Their levels are controlled by the rate of albumin synthesis, albumin fractional catabolic rate (FCR), and albumin distribution between the vascular and extravascular compartment. These in turn are affected by both nutrition and, since it is a negative acute-phase protein, by inflammation[9,10]. Although transferrin partly reflects nutritional status, an increase in its level in this study shows the presence of iron deficiency anemia in correlation to the Hb levels. While all of these measures are regarded as reflections of nutritional status, each is strongly associated with several indicators of inflammation[7]. Inflammation may both directly reduce measures that are used to establish nutritional status (lean body mass, serum albumin), and also affect nutritional intake, making it appear that the two are linked, while instead each has an independent effect. Qureshi et al has convincingly demonstrated that the activity of the acute phase response is an important predictor of low serum albumin in HD patients independently of nutritional factors[1].

Inflammation in HD patients leads to high risk of atherosclerotic CVDs has been proved by bregstrom et al[4]. However, inflammation contributes across the spectrum of cardiovascular disease, including the earliest steps in atherogenesis. This recognition has had a profound impact on the understanding of atherothrombosis as more than a disease of lipid accumulation, but rather as a disorder characterized by low-grade vascular inflammation[19]. Though the level of cholesterol in this study were low and Apo B was significantly high, this predicts future cardiovascular risk in chronic HD patients.HD patients undergoing routine laboratory assessment of hematologic and iron status include serum ferritin and other markers. Ferritin is both a marker of iron status and an indicator of inflammation or malnutrition in HD patients. Ferritin, an acute phase reactant, is elevated independently of iron stores in infection, inflammation, malignancy and chronic disease. Possible mechanisms for increases in ferritin during inflammation are by increased translation of mRNA ferritin subunits via IL-1β and TNF-α and reductions in iron mobilization[11,12]. An increase in Serum ferritin results from leakage of tissue ferritin, an intracellular iron storage protein. Serum ferritin is slightly different from tissue ferritin by the presence of iron or no iron. Liver dysfunction and other inflammatory factors may interfere with the synthesis and clearence thereby increasing serum ferritin levels with circumstances not related to iron metabolism. An activated acute phase process as represented by elevated levels of Serum Ferritin, CRP was identified to be a strong independent predictor of overall & cardiovascular mortality in HD patients besides age, low BMI, presence of diabetes, pre-existing CVDs and gender. The increase in hsCRP include intermittent stimulation by endotoxins originating from the dialysis water supply and artificial vein grafts or biocompatibility may play a role. The latter may activate an inflammatory process in CRF patients but the available data is inconsistent.

CONCLUSION

HD patients are in a higher oxidative state due to increased inflammation. Our results underline the potential role of an activated acute phase response that is an independent predictor of overall and cardiovascular mortality in patients on chronic HD. It showed that ferritin is increased independently of iron therapy which concludes that ferritin is more an acute phase reactant and is increased solely by inflammation in HD patients who are devoid of iron therapy. This strengthens the concept that serum ferritin is an imprecise indicator of iron stores in hemodialysis patients, and these increased levels of chronic inflammation may lead HD patients to at higher risk of Atherosclerotic CVDs. However, prospective long-term follow up studies are recommended in future to clarify the mechanism and links between high inflammation, Cardiovascular morbidity and mortality in chronic HD patients.

ACKNOWLEDGEMENT

The authors are grateful to dr. padmanabhan, department of nephrology for his advice and encouragement. We extend our sincere thanks to jeevanandhan and all the participants of our study.

REFERENCES

1. Qureshi AR, Alvestrand A, Danielsson A, Divino-Filho JC, Gutierrez A, Lindholm B, Bergstrom J : Factors influencing malnutrition in hemodialysis patients: Across-sectional study. Kidney Int 53:773-782, 1998
2. Kaysen GA, Stevenson FT, Depner TA : Determinants of Albumin concentration in

Hemodialysis patients. Am j Kidney Dis. 29:658-668 ; 1997
3. Zimmermnn J, Herlinger S, Pruy A, Metzger T, Wanner C: inflammation enhances cardiovascular risk and mortality in hemodialysis. Kidney Int. 55:648-658 ; 1999
4. Bregstrom J, Heimburger O, Lindholm B, Quershi AR: C-reactive protein as predictor for serum albumin and mortality in hemodialysis patients. J Am Soc Nephrol. 6:573-577 ; 1995
5. Kalantar-zadeh K, Rodriguez RA, Humphreys MH : Association between serum ferritin and measures of inflammation, nutrition and iron in hemodialysis patients.Nephrol Dial Transplant. 19:141-149 ; 2004
6. Stenvinkel P, Heimburger O, Paultre F, et al : Strong association between malnutrition, inflammation and atherosclerosis in chronic renal failure. Kidney Int. 55:189-1911 ; 1999
7. Kirchbaum B : Profiling hemodialysis patients with high ferritin levels. Clin Nephrol. 56:117-123; 2001
8. Wish JB. Assessing iron status : beyond serum ferritin and transferrin saturation. Clin J Am Soc Nephrol. 1(supp 1):S4-S8 ; 2006
9. Iseki K, Tozawa M, Yoshi S, et al : Serum C-reactive protein(CRP) and risk of death in chronic dialysis patients. Nephrol Dial Transpl. 14:1960-1999 ; 1999
10. Singh AK, Coyne DW, Shapiro W, Rizkala AR: Predictors of response to anemia treatment in hemodialysis patients with high serum ferritin and low transferrin saturation. Kidney Int. 1163-1171 ; 2007
11. Kwak EL, Larochelle DA, Beaumont C, Torti SV, Torti FM : Role of NF-kappa B in the regulation of ferritin H by tumor necrosis factor-alpha. J Biol Chem. 270:15285-15293 ; 1995
12. Rogers JT, Bridges KR, Durmowicz GP, Glass J, Auron PE, Munro HN. Transplantation control during the acute phase response: ferritin synthesis in response to interleukin-1. J Biol Chem. 265:14572-14578 ; 1990
13. Koch M, Kutkuhn B, trenkwalder E, Bach D, Grabensee B, Dieplinger H, Kornenberg F: apolipoprotein B, fibrinogen, HDL cholesterol and apolipoprotein (a) phenotypes predict coronary artery disease in hemodialysis patients. J Am Soc Nephrol. 8:1889-1898 ; 1997
14. Fishbane S, Kowalski EA, Imbriano LJ, Maesaka JK: The evaluation of iron status in hemodialysis patients. J Am Soc Nephrol. 7:2654-2657 ; 1996
15. Kalantar- Zadeh K, Lee GH: The fascinating but deceptive ferritin: to measure it or not to measure it in chronic kidney disease? Clin J Am Soc Nephrol. 1:S9-S18 ; 2006
16. David J. Hobbs, Allan B. Schwartz, Ed Gracely, Toros Kapoian, Adel R. Rizkala: volatility of elevated serum ferritin in anemic hemodialysis patients. JNephrol. 22: 553-560 ; 2009
17. Locatelli F, Canaud B, Eckardt KU, Stenvinkel P, Wanner C Zoccali C: Oxidative stress in end-stage renal disease: an emerging threat to patient outcome. Nephrol Dial Transplant. 18:1272-1280 ; 2003
18. Agoda LY, Eggers PW: Renal Replacement Therapy in the united states. Data from the united states renal data system 1995 annual data report. Am J Kidney Dis. 26 [supp 2] : S1- S186 ; 1995
19. Peter Libby, Paul M. Ridker and Attilio Maseri : Inflammation and Atherosclerosis. *Circulation.* 105:1135-1143 ; 2002
20. Attmann P-O, Alaupovic P, Tavella m, Knight-Gibson C : Abnormal lipid and apolipoprotein composition of major lipoprotein density classes in patients with chronic renal failure. Nephrol Dial Transplant. 11:63-69 ; 1996.