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## THE CORRELATION OF ANEMIA AND HEPcidIN SERUM LEVELS IN REGULAR HEMODIALYSIS PATIENTS WITH CHRONIC HEPATITIS C

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### ABSTRACT

End-Stage Renal Disease (ESRD) patients who undergo hemodialysis therapy are high-risk populations infected by the hepatitis C virus. Some studies have reported that hepcidin levels were decreased in patients with chronic hepatitis C. Hepcidin serum concentrations were also reported to increase in patients with renal failure in the line with increased severity of renal failure, which can cause the accumulation of hepcidin culminating in anemia due to iron deficiency. This study was to analyze the correlation of anemia and hepcidin serum levels in ESRD patients who underwent regular hemodialysis with chronic hepatitis C. This was an analytical observational study with cross-sectional design, conducted on 24 ESRD patients with chronic hepatitis C and 24 patients with ESRD without hepatitis who were undergoing regular hemodialysis therapy in the Adam Malik Hospital, Medan during July – September 2016. All study subjects were examined for full blood count and hepcidin serum levels. The result of the iron status was recorded from the patient's medical record. In this study, the mean hemoglobin was  $8.15 \pm 1.44$  g/dL, mean hematocrit  $25.42 \pm 4.53\%$ , median hepcidin levels 29.75 (4.92-359.49) in the ESRD patients with chronic hepatitis C and mean hemoglobin  $8.21 \pm 1.50$  g/dL, mean hematocrit  $25.25 \pm 4.37\%$ , median hepcidin levels 30.33 (11.65-141.53) in the ESRD patients without hepatitis. The Spearman's rho test showed a positive correlation that was significant between hepcidin and hemoglobin ( $r = 0.439$ ,  $p=0.032$ ), hepcidin and hematocrit ( $r = 0.021$ ;  $p=0.024$ ) in ESRD patients with chronic hepatitis C. This study showed a positive correlation between anemia and hepcidin serum levels in ESRD patients with chronic hepatitis C who underwent regular hemodialysis.

**Key words:** End-stage renal disease, anemia, hemodialysis, hepatitis C, nonhepatitis, hepcidin

### INTRODUCTION

Anemia is common in patients with Chronic Kidney Disease (CKD) especially in patients with End-Stage Renal Disease (ESRD) that undergo hemodialysis.<sup>1</sup> Anemia in patients with CKD can cause a decrease in oxygen supply and consumption, an increase in cardiac output, hypertrophy of the left ventricle, cardiac arrest, a decrease in cognitive skills, sexual and endocrinal dysfunction and suppression of the immune system that if it is not overcome, will cause a higher morbidity and mortality.<sup>2-4</sup> Prevalence of anemia in patients with chronic kidney disease according to the WHO is 84.5% with a prevalence in patients with chronic dialysis becoming 100% and 73.1% in pre-dialysis. In America, according to USRDS 2010, anemia in patients with stage 1-4 CKD was 51.8% and had a mean Hb in ESRD patients of 9.9 g/dL.<sup>5</sup> In Indonesia, there is no data of national anemia epidemiology.<sup>6</sup> End-stage renal disease is a clinical condition marked by a progressive decrease in kidney function that is static, in where the kidney fails to maintain fluid and electrolyte imbalance, until

a state or stage where permanent kidney replacement therapy is needed, namely kidney transplantation or adequate dialysis, either by Hemodialysis (HD) or Continuous Ambulatory Peritoneal Dialysis (CAPD).<sup>6-8</sup> Patients that need kidney replacement therapy raised two fold during this last decade. In America 2009 there were 116,395 new ESRD patients. More than 380,000 ESRD patients having regular hemodialysis.<sup>5</sup> Regular hemodialysis is defined as a HD that is performed regularly and is scheduled.<sup>9</sup> The longer an ESRD patient undergoes HD, the higher the risk of blood and iron loss.<sup>10</sup>

Hemodialysis is still the most used renal replacement therapy in Indonesia.<sup>11</sup> ESRD patients undergoing hemodialysis therapy are a population with a high risk to be infected with blood transmitted disease (blood-borne disease) like hepatitis C, hepatitis B, and HIV/AIDS.<sup>12,13</sup> Hepatitis C infection in patients undergoing hemodialysis is a health problem in both developed and developing countries. This is due to the hepatitis C infection increasing the numbers of liver cirrhosis and liver

cancer (hepatoma) that will increase morbidity and mortality.<sup>14</sup> There are several risk factors for hepatitis C infection in patients undergoing hemodialysis, including: poor management of infection prevention, low socio-economic conditions and high rates of blood transfusion and length of time undergoing hemodialysis with a very varied prevalence.<sup>15</sup>

Hepcidin is produced by the liver and serves as the main regulator of systemic iron hemostasis. Hepcidin controls the concentration of iron in plasma and is the distributor of iron in tissues by inhibiting the absorption of iron in the bowels, the recycling of iron by macrophages and mobilization of iron from iron storage in the liver.<sup>16,17</sup> When the kidney function is in a normal condition, the concentration of hepcidin in the urine is balanced with hepcidin in serum. A decrease in kidney function can decrease hepcidin excretion causing a build-up of hepcidin serum that ends up in iron deficiency anemia. The concentration of hepcidin is reported to be increased in patients with kidney failure even though it might also be caused by inflammation that often accompanies patients with kidney failure, as reported in a study by Ashby *et al.*, but patients without inflammation can have an increase in hepcidin that will keep on increasing in concordance with the degree of kidney failure.<sup>18-21</sup>

The concentration of hepcidin expression in chronic liver disease has a strong correlation with the concentration of iron deposits in the liver. In a study by Fujita *et al.* it was stated that the low concentration of hepcidin expression in chronic hepatitis C patients is related to the pathological mechanism where there is an increase in excess iron in chronic hepatitis C patients.<sup>22,23</sup> Girelli *et al.* reported a decrease in hepcidin serum in patients with chronic hepatitis C.<sup>24</sup> In Khadr *et al.* study, there was a decrease in hepcidin serum in patients with chronic hepatitis C.<sup>25</sup> Alsaran *et al.* stated that ESRD patients undergoing hemodialysis with chronic hepatitis infection, have a higher hemoglobin concentrations and hematocrit compared to patients without hepatitis.<sup>26-32</sup>

Based on the problems and results of the researches above, a research was done to find the correlation of anemia with hepcidin serum concentrations in patients undergoing regular hemodialysis that have chronic hepatitis C in the hemodialysis installation of the Adam Malik Hospital Medan.

## METHODS

This research was observational analytical with a

cross-sectional design done on 24 patients with ESRD and chronic hepatitis C and 24 ESRD patients without hepatitis that had regular hemodialysis therapy at the Adam Malik Hospital Medan from July – September 2016 who fulfilled the inclusion criteria. All research subjects had their complete blood count and hepcidin serum concentration examined. The results of the iron status were taken from the patients medical records.

Inclusion criteria of ESRD patients who had regular hemodialysis and had chronic hepatitis C (already infected with HDV >six months) and nonhepatitis and received Erythropoietin Stimulating Agents (ESA) therapy as was written in the medical records and who willing were to participate in the study by signing the informed consent. Exclusion criteria were patients who not were willing to sign the informed consent, patients who had malignancy, liver cirrhosis with a history of gastrointestinal bleeding and those who had HIV and was written in the medical record.

Ethical clearance was given by the Committee of Medical Research of the Medical Faculty of USU at the Adam Malik Hospital Medan. Informed consent was asked on paper by the subjects of the research. History taking and physical examination were done. The data and research results were recorded in a special research status. The complete blood count was done gradually using an automatic cell counter analyzer Sysmex XN-1000 with a flow cytometry method to see the anemia parameters (hemoglobin and hematocrit). The hepcidin serum concentration was done simultaneously after the serum samples were collected using ELISA and using the Chemwell® 2910 analyzer.

Data analysis was done using SPSS version 17.0 to see the relationship of anemia with hepcidin serum concentration, using Pearson correlation if the two groups of data were normally distributed and Spearman's rho correlation test if the data was not normally distributed. All the statistic tests were significant if the p was < 0.05.

## RESULTS AND DISCUSSION

Twenty-four patients with ESRD and chronic hepatitis C and 24 nonhepatitis ESRD patients who had regular HD twice a week at the Hemodialysis Installation of Adam Malik Hospital Medan in July 2016 had characteristics as in Table 1.

Data from Table 1 showed that 48 of the research subjects were grouped by age and sex. The youngest research subject was 37 years old and the eldest was 77 years old in ESRD patients with chronic C hepatitis undergoing regular HD and in nonhepatitis patients

with ESRD undergoing regular HD the youngest age was 34 years old and the eldest was 70 years old. The sex of the subjects were mostly males as much as 14 (58.3%) compared to females who were only 10 people (41.7%).

This research showed that ESRD patients with chronic hepatitis C and who underwent regular HD were caused mostly by hypertension nephropathy as much as 17 (70.8%), followed by Diabetes Mellitus (DM) as much as 6 (25%) and 1 person (4.2%) who had a kidney stone. In nonhepatitis ESRD patients, there were 16 (66.7%) with hypertension nephropathy, DM 6 (25%) and 2 (8.3%) with kidney stones. The lowest weight in patients with chronic Hepatitis C ESRD was 47 kg and 43 kg for nonhepatitis ESRD patients. The highest weight in ESRD patients with chronic C hepatitis was 80 kg and 74 kg in patients with nonhepatitis ESRD.

In Table 2 it can be seen that patients with chronic C hepatitis and ESRD had a mean hemoglobin concentration of  $8.15 \pm 1.44$  gr/dL, mean hematocrit of  $25.42 \pm 4.53\%$ , mean albumin of  $2.85 \pm 0.58$  gr/dL, median of hepcidin serum concentration 29.75

(4.92–359.49)pg/mL, ferritin median of 812.13 (28.31–4639.54) ng/mL, iron serum median 65.00 (21–185)  $\mu$ g/dL and TIBC median of 197.50 (83–285)  $\mu$ g/dL. In patients with nonhepatitis ESRD there was a mean hemoglobin concentration of  $8.21 \pm 1.50$  gr/dL, mean hematocrit of  $25.25 \pm 4.37\%$ , mean albumin of  $2.82 \pm 0.31$  gr/dL, median of hepcidin serum concentration 30.33 (11.65 – 141.53) pg/mL, ferritin median of 865.28 (105.00–3337.87) ng/mL, iron serum median 49.50 (9–190)  $\mu$ g/dL and TIBC median of 211.00 (106–276)  $\mu$ g/dL.

The results of Spearman's rho test showed a positive relation between hepcidin serum concentration followed by an increase in hemoglobin ( $r=0.439$ ) in ESRD patients with chronic C hepatitis, statistic tests showed a significant correlation between hepcidin serum concentration and hemoglobin ( $p=0.032$ ) in ESRD.

From Spearman's Rho test there was a positive relationship between hepcidin serum and hemoglobin ( $r=0.130$ ) in patients with nonhepatitis ESRD. Statistics showed an insignificant relationship between hepcidin serum and hemoglobin ( $p=0.544$ )

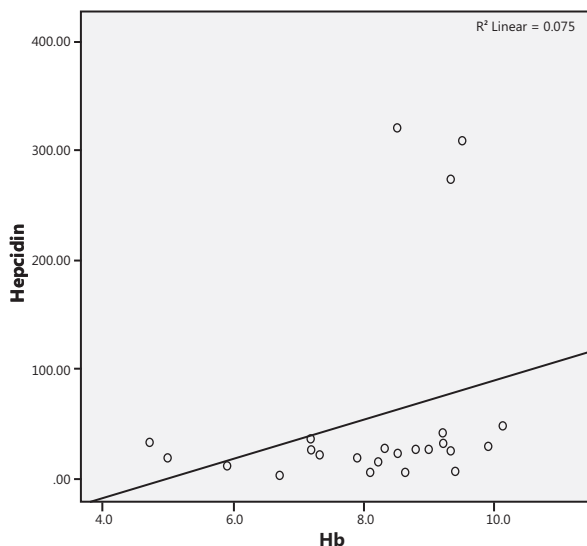
**Table 1.** Research subject characteristics

Characteristics	ESRD	
	Hepatitis C	Non hepatitis
n (people)	24	24
Sex		
Male	14(58.3%)	14 (58.3%)
Female	10(41.7%)	10 (41.7%)
Age (years old)		
Min–Max	37 – 77	34 – 70
( Mean $\pm$ SD )	$54.00 \pm 10.30$	$60.79 \pm 10.49$
Etiological diagnosis		
Hypertension	17	16
Diabetes mellitus	6	6
Kidney stone	1	2
Weight		
Min–Max	47 – 80	43 – 74
(Mean $\pm$ SD)	$60.79 \pm 9.56$	$59.50 \pm 6.56$

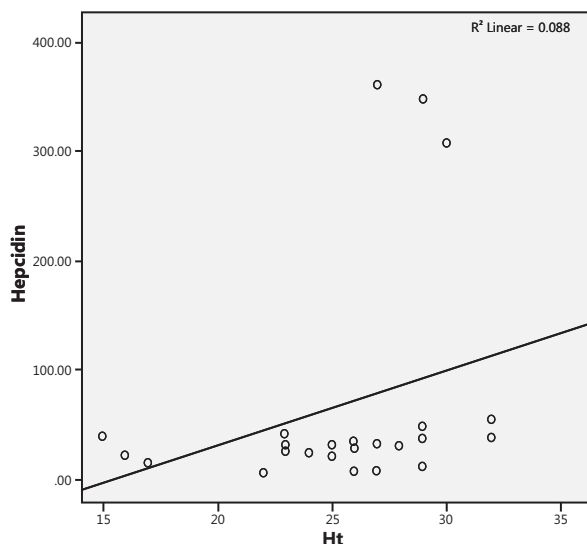
**Table 2.** Research subjects characteristics based on laboratory results

Characteristics	ESRD		P
	Hepatitis C	Nonhepatitis	
n (people)	24	24	
Hemoglobin (g/dL)	$8.15 \pm 1.44$	$8.21 \pm 1.50$	0.899*
Hematocrit (%)	$25.42 \pm 4.53$	$25.25 \pm 4.37$	0.898*
Albumin (g/dL)	$2.85 \pm 0.58$	$2.82 \pm 0.31$	0.830*
Hepcidin (pg/mL)	29.75 ( 4.92 – 359.49 )	30.33 (11.65 – 141.53)	0.688^
Ferritin	812.13(28.31 – 4639.54)	865.28 (105.00–3337.87)	0.665^
Serum iron	65.00 ( 21 – 185 )	49.50 ( 9 – 190 )	0.140^
TIBC	197.50 ( 83 – 285 )	211.00 (106 – 276 )	0.730^

The difference is significant if  $p < 0.05$ . Difference test using ^= Mann-Whitney U; \*= Unpaired t-test



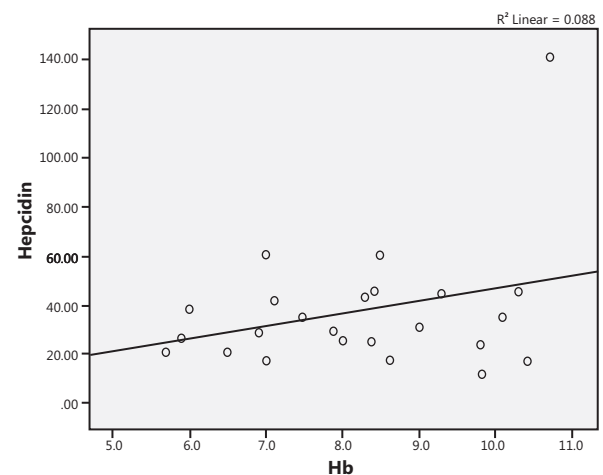
**Figure 1.** Graph of the relationship between hepcidin serum levels and hemoglobin in chronic hepatitis C ESRD patients



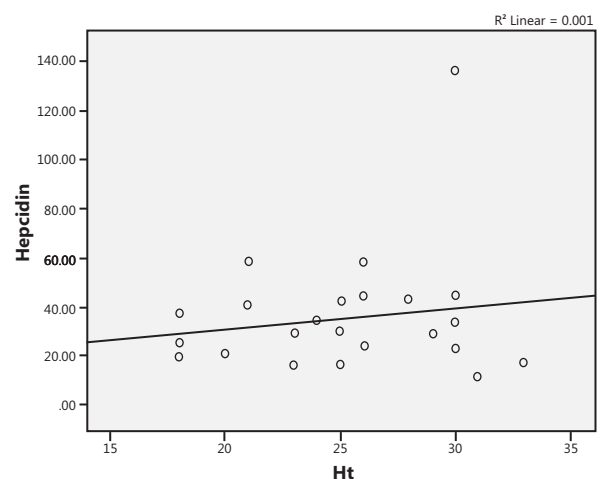
**Figure 2.** Graph of the relationship between hepcidin serum levels and hematocrite in chronic hepatitis C ESRD patients

in patients with nonhepatitis ESRD (Figure 1 and 2). There was a positive relationship between hepcidin serum concentrations and hematocrit ( $r=0.021$ ) in nonhepatitis ESRD patients, statistics showed that there was an insignificant relationship between hepcidin serum and hematocrit ( $p=0.924$ ) in nonhepatitis ESRD patients (Figure 3 and 4).

This research comprised 24 patients with chronic C hepatitis and ESRD with an age range of 37 – 77 years old and a mean of  $54.00 \pm 10.30$  years old, and 24 patients with nonhepatitis ESRD with an age range of 34 – 70 years old and a mean of  $60.79 \pm 10.49$  years old. Most of the research subjects were males, approximately 28 (58.3%), compared to females which were only 20 (41.7%). This was in concordance



**Figure 3.** Graph of the relationship of hepcidin serum concentrations and hemoglobin in nonhepatitis ESRD patients



**Figure 4.** Graph of the relationship of hepcidin serum concentrations and hematocrite in nonhepatitis ESRD patients

with the Zumrutdal and Sezgin study that had more males (66.6%) than females (33.4%).<sup>23</sup> The mean hemoglobin level was  $8.15 \pm 1.44$  gr/dL in chronic hepatitis C ESRD patients and  $8.21 \pm 1.50$  gr/dL in nonhepatitis ESRD patients. This was different from the results of Alsaran *et al.* stating that ESRD patients undergoing hemodialysis therapy with chronic hepatitis infection had a higher hemoglobin level compared to patients without hepatitis.<sup>26</sup> The mean hematocrit was  $25.42 \pm 4.53\%$  in chronic hepatitis CESRD patients and  $25.25 \pm 4.37\%$  in nonhepatitis ESRD patients. This was the same as results by Alsaran *et al.* that found chronic hepatitis C ESRD patients undergoing hemodialysis had a higher hematocrit than patients without hepatitis.<sup>26</sup> The median for hepcidin serum concentration was lower in chronic hepatitis CESRD compared with nonhepatitis ESRD patients, 29.75 (4.92-359.49) pg/mL and 30.33 (11.65-141.53) pg/mL. This was in concordance with



the study of Girelli *et al.* and Khadr *et al.* who reported a decrease in hepcidin serum concentration in chronic hepatitis C ESRD patients.<sup>24,25</sup>

This study found a positive relationship between hepcidin serum concentration and hemoglobin and was statistically significant ( $r = 0.439$ ;  $p = 0.032$ ) in chronic hepatitis C ESRD patients and a positive relationship for hepcidin serum and hematocrit that also was statistically significant ( $r = 0.459$ ;  $p = 0.024$ ) for chronic C hepatitis ESRD patients.

This study showed a positive relationship between hepcidin serum concentration and hemoglobin that was not statistically significant ( $r = 0.130$ ;  $p = 0.544$ ) in nonhepatitis ESRD patients and a positive relationship for hepcidin serum and hematocrit that was also not statistically significant ( $r = 0.021$ ;  $p = 0.924$ ) for nonhepatitis ESRD patients.

## CONCLUSION AND SUGGESTION

This study showed a positive relationship between anemia and hepcidin serum concentration in end-stage renal disease patients undergoing regular hemodialysis who were also infected with chronic hepatitis C. To see this relationship clearly, further studies must be done with higher samples and the dose of ESA given to the patients should be clarified. Iron supplements should be recommended to the patients participating in the study to see the role of hepcidin in overcoming anemia in ESRD patients with chronic hepatitis C.

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