

Evaluation the Iron Load in Chronic Hemodialysis Patients with Fibroscan: A Preliminary Study

Kronik Hemodiyaliz Hastalarında Demir Yükünüün Fibroscan ile Değerlendirilmesi: Öncül Çalışma

ABSTRACT

OBJECTIVE: Iron preparations are frequently used in hemodialysis (HD) patients and iron may accumulate liver and other tissues. Noninvasively methods are needed to detect liver iron accumulation in HD patients. Hepatic iron accumulation with Fibroscan was shown in non-renal population. In this study, we aim to investigate whether or not the hepatic iron load can be determined with Fibroscan in hemodialysis patients.

MATERIAL and METHODS: 42 chronic HD patients included this study. Serum iron, iron binding capacity, ferritin and transferrin saturation were used to determine iron status. Liver stiffness was measured by an experienced gastroenterologist with Fibroscan device.

RESULTS: While mean Fibroscan value was 9,15 kPa, ferritin was 565,99 mg/dl. Fibroscan value were positive correlated with transferrin saturation and ferritin but negative correlated with albumin. In multiple regression analysis, it was observed that only ferritin and albumin levels related with Fibroscan value.

CONCLUSION: This study showed that the stiffness of the liver increasing while the ferritin value increasing. This result might be due to iron accumulation in the liver.

KEY WORDS: Anemia, Fibroscan, Hemodialysis, Hepatic iron

ÖZ

AMAÇ: Hemodiyaliz (HD) hastalarında demir preparatları sıklıkla kullanılmaktadır ve belkide bu demir karaciğer ve diğer organlarda birikmektedir. HD hastalarında karaciğerde demir birikimini noninvaziv olarak değerlendirecek bir metoda ihtiyaç vardır. Non renal hasta popülasyonunda Fibroscan ile karaciğer demir yükünü değerlendiren çalışmalar mevcuttur. Çalışmada Fibroscan ile HD hastalarında karaciğer demir yükünün ölçülüp ölçülemeyeceğini araştırdık.

GEREÇ ve YÖNTEMLER: Çalışmaya 42 kronik HD hastası dahil edildi. Demir içeriği, serum demir, demir bağlama kapasitesi, transferin saturasyonu ve ferritin değeri ölçülerek değerlendirildi. Karaciğer sertliği tecrübeli bir gastroenterolog tarafından Fibroscan cihazı ile ölçüldü.

BULGULAR: Ortalama Fibroscan değeri 9,15 kPa, ferritin ise 565,99 mg/dl idi. Fibroscan değeri transferin saturasyonu ve ferritin ile pozitif, albümin ile negatif korele idi. Çoklu regresyon analizinde sadece ferritin ve albümin Fibroscan değeri için belirleyici olarak bulundu.

SONUÇ: Çalışma serum ferritin değeri arttıkça karaciğer sertliğinin arttığını gösterdi. Bu, karaciğerde demir birikiminin bir sonucu olabilir.

ANAHTAR SÖZCÜKLER: Anemi, Fibroscan, Hemodiyaliz, Karaciğer demiri

INTRODUCTION

Anemia is a frequent complication in hemodialysis (HD) patient population. Intravenous iron (Fe), and erythropoietin

preparations are used in its treatment. In iron treatment, it should be targeted that the ferritin level is over 200 mg/dl and the serum transferrin saturation (TSAT) is over 20%

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according to NKF-KDOQI guideline (1). However, extremely high serum ferritin levels were shown in many hemodialysis patients. There might be insufficiencies in the transfer of the stored iron to circulation from the liver for erythropoiesis due to various reasons. Meanwhile, excessive iron use may lead to dysfunctions in many organs, mostly in the liver. The gold standard test in measuring the hepatic iron load is liver biopsy and determining the Fe concentration in dry liver tissue with the Atomic Absorption Spectrophotometry Method (2,3). However, this is an invasive method. New methods that will test the hepatic iron load in easy and reliable ways are being developed. Recently, it has been demonstrated that the liver iron load can be determined in a non-invasive method with Magnetic Resonance Imaging (MRI) (4-7). However, MRI is a high cost testing method and it is difficult to obtain in every clinic.

Recently, Fibroscan (Transient Elastography) is an ultrasonographic method that has been used to evaluate hepatic fibrosis. Hepatic elasticity is measured by using shear wave method and this method determines the fibrosis level with a non-invasive way (8,9). It is generally used in determining the fibrosis level in diseases like chronic hepatitis and Non-Alcoholic Steato-Hepatitis (NASH) or used in order to evaluate the response to the treatment. Several studies were performed to evaluate the hepatic iron accumulation with Fibroscan in non-renal population (10-13). The excessive iron accumulation in liver tissue in HD patients may be determined by measuring the stiffness of the liver with Fibroscan. The role of Fibroscan on evaluate of the hepatic iron load has not been well studied in hemodialysis patients. In this study we have investigated, for the first time in the literature, whether or not the hepatic iron load can be determined with Fibroscan in hemodialysis patients.

MATERIAL and METHOD

This cross-sectional study was conducted in Kahramanmaraş Sutçu Imam University Medical Faculty, Dialysis Unit. Chronic hemodialysis patients who were over the age of 18 and who were receiving hemodialysis treatment for at least 6 months were included in the study. Patients who had chronic liver disease, chronic viral hepatitis (HBV, HCV), alcohol use, polycystic renal disease together with liver disease, and active infection were not included in the study. The demographic data of the patients like age, gender, the duration in which they were receiving dialysis treatment, chronic renal failure (CRF) etiology, diabetes mellitus (DM) and the existence of hypertension (HT), and the laboratory parameters which were received monthly as a routine were obtained from the patient files. The serum iron level (Fe), Total Iron Binding Capacity (TIBC), Transferrin Saturation (TSAT) and Ferritin levels were used as the iron parameters of the patients. The monthly iron dosages and the weekly erythropoietin dosages used were recorded. The liver stiffness was measured with a Fibroscan 502 TOUCH F60453 brand device and XL 9 90457 probe by a single gastroenterologist, who was experienced in this field.

The measurements were made when the patients were in supine position and the right arm in full abduction, from the right lobe of the liver, from the midaxillar line and intercostal gap. 10 measurements in average were performed for each patient, and the average Fibroscan values were obtained as kilopascal (kPa) and the final results were recorded. The written consents of the patients were received. The ethical approval of the study was received from Kahramanmaraş Sutçu Imam University, Faculty of Medicine, Ethical Board.

Statistical Analysis

The constant variables of the patients like age, dialysis duration, and laboratory parameters were recorded as mean \pm SD; and the parameters like the gender, DM and HT frequency were recorded as ratios. The relation between the mean Fibroscan and iron parameters was analyzed with Spearman Correlation Test, and the Correlation Coefficients and the *p* values were obtained. The factors that influence the mean Fibroscan value were evaluated with multiple regression analysis. The results are given with *p* value and 95% Confidence Interval. The *p*<0,05 value was accepted as being statistically significant.

RESULTS

A total of 42 hemodialysis patients were included in the study. The mean age of the patients was 51.2 \pm 15.5 years; and 56.8% of the patient population was male. The average dialysis duration was 43.5 \pm 44.9 months and the BMI was 25.6 \pm 6.1 kg/m². The demographic data of the patients and the laboratory parameters are summarized in Table I and II. The average Fibroscan value was 9.15 kPa. In the correlation analysis, the Fibroscan value showed positive correlation with TSAT (*p*=0.007; *r*=0.41); ferritin (*p*=0.01; *r*=0.36); negative correlation with TIBC (*p*=0.003; *r*=0.44); and albumin (*p*<0.001; *r*=-0.52) (Table III). No correlation was determined between the serum Fe and Fibroscan. The ferritin and TIBC showed reverse correlation (*p*<0.001; *r*=-0.52). The TSAT showed positive correlation with Fe (*p*<0.001; *r*=0.81), and reverse correlation with TIBC (*p*=0.01; *r*=-0.50).

In multiple regression analysis, the albumin (*p*=0.002; 95% CI: -19.7- 4.6) and ferritin (*p*=0.02; 95% CI: 0.001-0.015) were found related with Fibroscan value; while the TSAT was not found related (*p*=0.21) (Table IV).

DISCUSSION

Extremely high ferritin values is frequently seen in chronic hemodialysis patients despite the extreme accumulation of iron. Although the gold standard test to show the liver iron accumulation is the liver biopsy, this is not suitable for using in clinical practice since it is an invasive method. Non-invasive, easily repeatable, and cheap method is needed to be used in demonstrating the iron load in this population. In this study, we evaluated the iron load in the liver in chronic hemodialysis patient population with Fibroscan for the first time. In our study,

Table I: The Demographic data of the patient population.

Age (Years)	51.2±15.5
Gender M/F	56.8/43.2 (24/18)
Duration of dialysis (Months)	43.5±44.9
EPO dosage (Units/week)	7451.6±2656.2
Iron dosage (mg/week)	117.1±38.2
BMI (kg/m ²)	25.6±6.1
CRF etiology	
DM	34.1
HT	29.5
CGN	4.5
PCK	11.4
Amyloidosis	2.3
Other	6.8
Unknown	2.3

BMI: Body mass index, **EPO:** Erythropoietin, **CRF:** Chronic renal failure, **CGN:** Chronic glomerulonephritis, **PCK:** Polycystic kidney disease.

it was observed that there was a positive correlation between the Fibroscan values and the TSAT and ferritin levels. High ferritin and TSAT levels are frequently observed in chronic hemodialysis patients. In this study, we showed that as the ferritin and TSAT levels increase, the stiffness of the liver increases in hemodialysis patients.

Fibroscan is an imaging method used in evaluating the liver fibrosis. As a principle, it evaluates the stiffness of the liver by using shear wave method, and is used to demonstrate the fibrosis in a non-invasive way. However, liver elasticity may be influenced not only by fibrosis but also by the accumulation of various materials in the liver tissue. Arena et al. 2008 (14) showed that the stiffness of the liver increased in patients with acute viral hepatitis by using Fibroscan. Necro-inflammatory lesions occurring in the liver may increase the stiffness of the liver in the absence of fibrosis. Trabut et al. (15) showed that the Fibroscan value of 137 patients who were hospitalized for the purpose of giving up alcohol decreased from 7,2 kPa to 6,1 kPa only in 7 days on which the subjects did not drink alcohol. Stefanescu et al. (16) showed that the Fibroscan values decreased with the copper chelation treatment in patients with Wilson's disease with no fibrosis. According to these studies, it is understood that the accumulation diseases in except to fibrosis also increases stiffness of the liver, and may be detected with Fibroscan. Based on these data, we focused on the idea that the determination of iron accumulation may be possible with Fibroscan in HD population who receive intensive iron

Table II: Laboratory data of the patient population.

n=42	Mean±SD
Urea (mg/dl)	52.7±14.9
Cr (mg/dl)	7.52±1.99
Uric Acid (mg/dl)	5.7±1.2
Albumin (gr/dl)	3.67±0.33
Ca (mg/dl)	8.61±0.67
P (mg/dl)	4.6±1.0
AST (U/ml)	19.6±8.0
ALT (U/ml)	19.0±9.0
Hb (gr/dl)	10.6±1.3
Hct (%)	32.7±3.8
Triglyceride (mg/dl)	154.1±93.0
Ldl (mg/dl)	74.7±26.5
Fe (mcg/dl)	63.18±22.1
TIBC (mg/dl)	232.61±34.77
TSAT (%)	27.16±11.11
Ferritin (mg/dl)	565.99±339.74
Fibroscan (kPa)	9.15±9.04
PTH (pg/ml)	516.6±503.1
Kt/V	1.57±0.16
URR (%)	72.2±5.4

PTH: Parathyroid hormone, **URR:** Ure reduction rate.

Table III: Correlation of fibroscan value with iron parameters and laboratory parameters.

Fibroscan (kPa)	R	p
Fe	0.006	0.9
TIBC	-0.44	0.003
TSAT	0.41	0.007
Ferritin	0.36	0.01
Albumin	-0.52	<0.001

Table IV: Factors that related with Fibroscan value in multiple regression analysis.

	p	95% Confidence Interval	B
TSAT	0.21	0.08-0.36	0.14
Ferritin	0.02	0.001-0.015	0.008
Albumin	0.002	-19.7- 4.6	-12.1

treatment. In our study, when the factors that are related with the stiffness of the liver were examined in multiple regression analysis and it was observed that only the ferritin and albumin levels were found to be related with the Fibroscan values. TSAT, on the other hand, showed no meaningful relation with the Fibroscan value. According to these results, the stiffness of the liver increasing while the ferritin value increasing makes us think that the accumulation of the iron in the liver decreases the elasticity. The strong reverse correlation with albumin may probably be explained with the decrease in the synthesis capacity of the albumin as a result of the iron accumulating in the liver. The relationship between iron parameters and fibrosis was evaluated with Fibroscan in the non-renal patient population. Parikh et al. (10) showed a strong relation between the ferritin and Fibroscan values in their study in which 55 non-alcoholic fatty liver patients proven with biopsy were compared with 50 healthy individuals in the control group. However, in the biopsy group, 34 patients having fibrosis and 6 patients being at the cirrhosis stage decreases the reliability of their results because of the fibrosis having an effect on Fibroscan. In our study, on the other hand, the absence of biopsy group is limitation of our study, and the issue of whether fibrosis accompanies iron accumulation is not possible to know exactly. The possible development of fibrosis in our patients due to iron accumulation may explain the increase in the Fibroscan value. For this reason, according to our study, although it is not possible to claim definitely that the iron accumulation can be detected with Fibroscan, but our study may lead the way for future studies. Besides, serum ferritin levels were previously used as the indicator of fibrosis (17). Musallam et al. (11) conducted a study and compared 42 beta thalassemia patients who received chelation treatment and those who did not. In their study, the ferritin levels showed a meaningful decrease in the group who received chelation treatment, and the Fibroscan values also decreased at a meaningful level. However, significant increases were detected in the ferritin and Fibroscan values in the group who did not receive chelation treatment. It is a known that fibrosis is a pathologic process that is not reversible; and in their study it was demonstrated that the decrease in the liver iron load with chelation corrected the stiffness of the liver with Fibroscan. Similarly, we also showed that as the ferritin level increased so did the Fibroscan value. Lupşor (12) conducted a study in which he evaluated the Fibroscan values of 324 chronic HCV patients with histopathology, and showed that the liver elasticity influenced by steatosis and inflammatory activity -aside from fibrosis- also; however, was not influenced by iron accumulation. They explained that their finding with the iron showing mostly intracellular accumulation and the elasticity being influenced mostly by extracellular matrix accumulation. However, steatosis is also an intracellular accumulation and this explanation is not sufficient. The major limitations of our study are the small sample size and the lack of histopathological evaluation. Adhoute et al. (13) conducted a study in which they compared the patients who had hemochromatosis and the patients

evaluated for high levels of liver enzyme levels with biopsy and showed no fibrosis, and found that the Fibroscan values of both groups were similar. However, very few of the patients in the hemochromatosis group were newly diagnosed patients, and the number of the patients with extremely high ferritin levels was extremely low. The Fibroscan values of the patients who were newly diagnosed and who had very high ferritin levels were not found to be different from the patients with iron deficiency. Despite important limitations, our study has the results for the first time showing that it is possible to detect the hepatic iron load in hemodialysis patients with Fibroscan.

In conclusion, the stiffness of the liver, which has the most frequent iron accumulation in a patient population like HD patients who needs to receive regular iron treatment, can be evaluated with Fibroscan, which is a non-invasive method, the excessive iron accumulation may be detected; and the iron treatment can be review before any liver damage occur.

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