ORIGINAL ARTICLE

TJG
The Turkish Journal of Gastroenterology

Serum iron parameters in cirrhosis and chronic hepatitis: Detailed description

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Background/aims: *Serum iron parameters are affected by liver disorders. It is believed that the tests are unreliable in chronic liver disease, and systemic iron overload should be evaluated histologically in these patients. However, the effect of severity of chronic liver disease on serum iron parameters has not been evaluated. Similarly, differences between liver disease- and iron overload-related iron parameter changes have not been clarified. We aimed to describe the effect of severity of chronic liver disease on serum iron tests and to elucidate the differences of liver disease- and iron overload-related iron parameter changes.* ***Methods:*** *Commonly used serum iron parameters were studied in patients with cirrhosis, chronic viral hepatitis and in persons with confirmed hemochromatosis. Cirrhosis cases were categorized according to Child-Pugh classification.* ***Results:*** *We found that cirrhotic persons of any Child-Pugh class had deviations from normal results. Patients with chronic hepatitis had normal serum iron parameters. Total iron binding capacity decreased as liver disease progressed from hepatitis toward Class C cirrhosis ($r= –0.53$, $p<0.001$). Changes in ferritin and transferrin saturation were essentially opposite to this trend ($r=0.3$, $p=0.01$ and $r=0.47$, $p<0.001$, respectively). Serum iron level was lower in cirrhosis compared to hepatitis. Increased transferrin saturation and ferritin levels resembling iron overload were limited to Class C cirrhotics. Patients with true iron overload could be easily differentiated from these cases by hyperferremia.* ***Conclusion:*** *Aberrant serum iron test results indicate cirrhotic stage in chronic liver disease. Cirrhosis and systemic iron overload cause characteristically different changes in serum iron parameters.*

Key words: Iron, hepatitis, cirrhosis, hemochromatosis

Siroz ve kronik hepatit'te serum demir parametreleri: Detaylı değerlendirme

Amaç: *Serum demir test sonuçları karaciğer hastalıklarından etkilenirler. Bu testlerin kronik karaciğer hastalığında güvenilmez oldukları ve bu hastalarda sistemik demir yüklenmesin histolojik olarak değerlendirilmesi gerektiği genel bir inanıştır. Buna karşılık, kronik karaciğer hastalığı şiddetinin serum demir parametrelerine etkisi literatürde yayınlanmış bir konu değildir. Benzer şekilde, karaciğer hastalığına bağlı serum demir parameter değişiklikleri ile demir yüklenmesine bağlı değişikliklerin farkları belli değildir. Bu çalışmada belirtilen iki husus açığa kavuşturulmaya çalışılmıştır.* ***Yöntem:*** *Siroz, kronik viral hepatit ve kanıtlanmış hemokromatozisi olan hastalarda sık kullanılan serum demir testleri çalışıldı. Siroz hastaları Child-Pugh sınıflamasına göre gruplandı.* ***Bulgular:*** *Bütün Child-Pugh gruplarındaki sirotik hastalarda normal değerlerden farklılıklar gözlendi. Kronik hepatit hastalarında ise serum demir testleri normaldi. Karaciğer hastalığı hepatitten klas C siroza doğru ilerledikçe total demir bağlama kapasitesi azalıyordu ($r= –0.53$, $p< 0.001$). Ferritin ve transferin saturasyonunda bu eğilimin tersi yönünde değişiklikler gözlendi (sırasıyla $r= 0.3$, $p= 0.01$ ve $r= 0.47$, $p< 0.001$). Serum demir düzeyi sirozlu hastalarda hepatite nazaran daha düşüktü. Demir yüklenmesini andıran artmış transferin saturasyonu ve ferritin düzeyleri sadece klas C sirotik hastalarda izlendi. Gerçek demir yüklenmesi hastaları hiperferremi sayesinde bu hastalardan kolaylıkla ayırt edilebiliyordu.* ***Sonuç:*** *Aberran serum demir test sonuçları sirotik aşamada kronik karaciğer hastalığına işaret ederler. Siroz ve sistemik demir yüklenmesine bağlı serum demir test değişiklikleri karakteristik farklılıklar gösterirler.*

Anahtar kelimeler: Demir, hepatit, siroz, hemokromatozis

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Manuscript received: 12.09.2010 **Accepted:** 10.08.2011

Turk J Gastroenterol 2011; 22 (6): 606-611
doi: 10.4318/tjg.2011.0323

INTRODUCTION

The liver is an important organ in iron homeostasis. Besides its involvement in iron storage, the liver also produces transferrin and hepcidin, an iron carrier protein in plasma and a hormone regulating iron metabolism, respectively (1,2). Another aspect of the relationship between iron and the liver is that this organ is one of the main targets in hemochromatosis (3). Serum iron (SI), total iron binding capacity (TIBC) and ferritin levels are the principal tests used in the evaluation of iron burden. Another frequently used parameter, transferrin saturation (TS), is calculated by dividing SI level by TIBC, and it shows the percent saturation of transferrin.

Testing and understanding serum iron parameters in liver disorders are important for different reasons: 1) Serum TS and ferritin levels are used for the screening of hereditary hemochromatosis (4). 2) It has been proposed that iron might be important for progression of liver fibrosis in viral hepatitis, and serum iron parameters, especially ferritin level, might reflect hepatic iron accumulation (5). 3) Anemia is very frequent in cirrhotic patients for many different reasons including iron deficiency (6). Identification of iron deficiency in these patients is especially important, because it is an easily correctable cause of anemia.

Total iron binding capacity (TIBC) level (i.e., transferrin activity) may change in hepatic disorders as transferrin is produced in the liver (7,8). Ferritin is increased in many patients with acute and chronic liver diseases (CLDs) (7-9). Therefore, serum iron parameters may not truly reflect iron homeostasis in hepatic disorders. It has been proposed that serum iron parameters were unreliable in CLD, and that systemic iron overload should be confirmed histologically in these patients (10,11). However, the effect of the severity of hepatic compromise on the test results has not been clearly defined in any study. Similarly, differences between liver disease- and iron overload-related iron parameter changes have not been clarified. Previous studies related to iron homeostasis in CLDs might be confounded by difficulties in the diagnosis of hereditary hemochromatosis. Currently, this disease can be easily defined by genetic testing. We aimed to describe the effect of CLD severity on serum iron tests in patients with different Child-Pugh stages of liver cirrhosis unrelated to hemochromatosis and with chronic viral hepatitis and to elucidate differences in liver disease- and iron overload-related iron parameter changes.

MATERIALS AND METHODS

Patients, Controls, and Clinical and Lab Evaluations

Sequential patients with cirrhosis admitted to the Gastroenterology Department within a 10- month period were included in the study. The control groups were comprised of chronic hepatitis patients of similar age and gender, presenting within the same period, and age group and gender-matched healthy volunteers. It was aimed to have similar numbers of cirrhosis cases and controls, keeping in mind that cirrhosis cases were to be divided in three Child-Pugh subgroups. Cirrhosis was diagnosed based on the clinical, laboratory and ultrasonography findings. All cases of chronic viral hepatitis were assessed histologically. Fasting plasma or serum samples for iron, TIBC, ferritin, and parameters necessary for determining Child-Pugh scores were drawn from the patients in the morning. Alpha-fetoprotein level, hepatic ultrasound and computed tomography, if necessary, were used for the screening of hepatocellular carcinoma.

A patient group with transfusion-associated systemic iron overload due to thalassemia or hematological neoplasia was also evaluated for iron parameters in order to detect a pattern of iron parameter changes in cases with confirmed hemochromatosis. These patients had been followed in Hacettepe University School of Medicine, Department of Hematology. Confirmation of the hemosiderosis by previous liver biopsy and/or magnetic resonance imagining was required for inclusion in the iron overload group.

Serum iron (SI) and TIBC were tested by automated Roche/Hitachi analyzer system (Roche Diagnostic, Mannheim, Germany). This method is based on ferro zinc method without deproteinization. Serum ferritin measurement was performed by chemoimmunometric method (Immunolite autoanalyzer, Diagnostic Products Corp., Los Angeles, CA). Serum TS was calculated by dividing serum iron by TIBC.

Exclusion Criteria

Exclusion criteria for the patients and controls included steatohepatitis, iron or vitamin deficiencies, malignant diseases other than hepatoma, chronic infectious or inflammatory diseases, acute bleeding or red blood cell transfusion within the last three months, and chronic renal failure. Iron deficiency was defined both by standard criteria (TS <15% and ferritin <20 µg/L) and as proposed

by Intragumtornchai et al. (12) (ferritin <50 ng/ml) in cirrhosis patients. Statistical evaluations were made for each of these two definitions. Patients with additional hematologic problems known to cause anemia were also not included in the study. Control cases also met these criteria. Child-Pugh classification was made as previously described (13).

Statistics

The Statistical Package for the Social Sciences (SPSS) 10.0 for Windows (SPSS Inc., Chicago, IL) software was used for statistical calculations. Correlations between iron parameters and the Child-Pugh classification were calculated by the Spearman's correlation analysis. Group ratios were compared by the chi-square test. Means of two or more than two groups were compared by the Mann-Whitney U and the Kruskal-Wallis H tests, respectively. Nonparametric tests were preferred as there were generally fewer than 30 cases in the statistical groups. Statistical significance was defined by a P value lower than 0.05.

RESULTS

Demographic Data

Twenty-one CLD cases were eliminated due to exclusion criteria. Eighty-nine patients with CLD (71 hepatic cirrhosis, 18 chronic hepatitis) and 20 healthy control subjects were included in the study. Demographic data of the patients and controls are presented in Table 1. Distributions of age, gender and causes of liver disease were identical in the different liver diseases and control groups.

Serum Iron Parameters in Different Etiological Groups of Cirrhosis and Hepatitis

Serum iron (SI) and TIBC levels were lower in alcoholic cirrhosis patients compared to viral cirrhosis cases (p=0.05). Serum iron parameters did not change in the other etiological groups of cirrhosis. Further, all parameters were similar in the hepatitis B versus C cases (data not presented).

Serum Iron Parameters in Different Child-Pugh Groups vs Hepatitis vs Controls

Serum iron (SI), TIBC, ferritin, and TS levels were statistically not different in controls and chronic hepatitis cases. SI and TIBC levels were lower than controls in all Child-Pugh groups of cirrhosis. TS and ferritin levels were higher than controls in only Group C cirrhotic persons (Table 2). The results were similar when alcoholic cirrhosis cases were excluded, except that serum ferritin level was higher in all cirrhosis groups.

Serum Iron Parameters in Different Child-Pugh Groups

Total iron binding capacity (TIBC) decreased, and TS and ferritin levels increased as Child-Pugh class progressed ($p< 0.001$, $p< 0.001$, $p=0.02$, respectively) (Table 2; Figure 1). SI level did not change between Child-Pugh groups. The correlation coefficients were – 0.53, 0.47 and 0.30 for correlations of TIBC, TS and ferritin with Child-Pugh class, respectively ($p< 0.001$, $p< 0.001$ and $p=0.01$, respectively).

Transferrin saturation (TS) exceeded the upper limit of 50% in 21 (21/71, 29.5%) of the cirrhotic patients. None of these cases was in the Child-Pugh Class A. Only 1 was in Class B (1/15, 6.6%). Nearly all of them were in the Class C group (20/38, 52.6%). Elevated TS value was found in only 1 of the control subjects (1/20, 5%). No patient with chronic hepatitis had a TS value greater than 50%.

Total iron binding capacity (TIBC) was decreased in 19 of the 21 cases (90.4%) with an elevated TS level. Elevated SI and ferritin levels were found in

Table 1. Demographic data of the patients and controls

	Cirrhosis Child-Pugh Stage				Hepatitis	Controls	Iron overload
	A (N= 18)	B (N= 15)	C (N= 38)	Total (N= 71)	(N= 18)	(N= 20)	(N= 14)
Age (mean±SD)	54±16	55±10	50±15	52±14	47±11	49±9	33±10
Gender (F/M)	8/10	7/8	18/20	33/38	8/10	9/11	6/8
Cirrhosis etiology							
Hepatitis B	7	7	14	28	11		
Hepatitis C	4	4	10	18	7		
Alcohol	3	2	5	10			
Cryptogenic	3	2	6	11			
Others	1		3	4			
Cases with hepatoma	5	2	7	14			

Table 2. Serum iron parameters in different cirrhosis groups, hepatitis patients and controls

	Cirrhosis Child-Pugh Stage (n=71) A (N= 18)	B (N= 15)	C (N= 38)	Hepatitis (N= 18)	Controls (N= 20)	Iron overload (N= 14)
SI (40-160 µg/dl)	72±26*	77±43@,§	89±34‖,Ψ	120±32	110±27	234±38
TIBC (205-450 µg/dl)	291±65*	252±75*	193±75*	394±32	387±40	250±38
TS (15-50%)	26±10	30±12	53±26**,Ψ	30±8	28±8	93±5
Ferritin (20-300 ng/ml)	198±254@@	161±161@@	366±396*	68±63	80±40	4096±2989

Statistically significant comparisons between Child-Pugh groups and controls or hepatitis patients are indicated.

* p≤ 0.001 Vs controls and hepatitis cases, @ p< 0.01 Vs controls, § p≤ 0.001 Vs hepatitis cases, ‖ p< 0.05 Vs controls, Ψ p< 0.01 Vs hepatitis cases, ** p≤ 0.001 Vs control cases, @@ p< 0.05 Vs hepatitis cases

SI: Serum iron. TIBC: Total iron binding capacity. TS: Transferrin saturation.

1 (1/21, 4.7%) and 13 (13/21, 61.9%) cases, respectively. Simultaneously elevated SI and ferritin was not present in any of these cases. Simultaneously elevated TS (53-93%, mean±SD= 71±13) and ferritin (311-2000 µg/L, mean±SD= 637±463) was present in 13 cirrhotic patients. All of them were Class C cirrhotics.

Presence of hepatoma did not affect any of the serum iron parameters (data not presented).

Patients with systemic iron overload included 14 patients with transfusional hemosiderosis (Table 2). Cirrhosis was not present in any case of systemic iron overload. Associated chronic hepatitis C was present in 3 cases. All of the 14 patients had elevated SI, TS and ferritin. Only 1 of them had decreased TIBC.

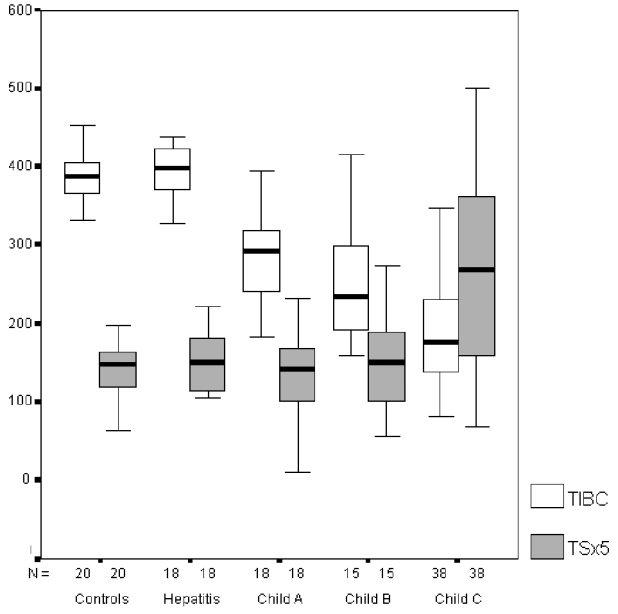

Figure 1. TIBC decreased and TS increased as Child-Pugh class progressed. TS values were multiplied by 5 to be shown on the same scale with TIBC.

Iron Deficiency Defined as <50 ng/ml Ferritin

When iron deficiency was defined as <50 ng/ml ferritin, all of the results were essentially similar to the previous calculations. One exception was that serum ferritin was more prominently elevated in all Child-Pugh groups compared to both controls and hepatitis cases (Table 3). Additionally, TIBC and TS were better correlated with Child-Pugh class. The correlation coefficients were – 0.57 and 0.54, respectively (p<0.001 for both correlations).

DISCUSSION

We found that aberrant serum iron test results clearly indicate the cirrhotic stage of CLD. Previously, some other authors also observed the association of aberrant serum iron tests with advanced stage of liver disease, defined by increased fibrosis and/or cirrhosis (14-16). Cirrhotic patients of any Child-Pugh class had deviations from normal results. This means that all Child-Pugh groups of cirrhosis had decreased SI and TIBC and increased ferritin levels. However, increased TS was essentially found in Class C cirrhotics. TIBC decreased as liver disease progressed from hepatitis toward Class C cirrhosis. Changes in ferritin and TS were essentially opposite to this trend. SI level was lower in cirrhosis compared to hepatitis.

In many advanced cirrhosis cases, TS and ferritin were simultaneously elevated, which may lead to suspicion of iron overload. All of the cases with simultaneously increased TS and ferritin were Class C cirrhotics. SI was invariably increased in systemic iron overload. This trend was also present in a limited number of cases of hemochromatosis with associated chronic hepatitis C. Although SI was elevated in some CLD cases, no patient had simultaneously elevated TS, ferritin and SI. These

Table 3. Serum iron parameters in different cirrhosis groups, hepatitis cases and controls when iron deficiency was defined by a ferritin value <50 ng/ml

	Group A (N= 12)	Group B (N= 12)	Group C (N= 33)	Hepatitis (N= 18)	Controls (N= 20)	Iron overload (N= 14)
SI (40-160 µg/dl)	80±23*	78±47*	94±34@,§	120±32	110±27	234±38
TIBC (205-450 µg/dl)	265±48‖	245±81‖	175±57‖	394±32	387±40	250±38
TS (15-50%)	30±8	31±12	58±24‖	30±8	28±8	93±5
Ferritin (20-300 ng/ml)	283±276‖	193±166*	418±401‖	68±63	80±40	4096±2989

Statistically significant and some other important comparisons between Child-Pugh groups and controls or hepatitis cases are indicated.

* p≤ 0.01 Vs controls and hepatitis cases, @ p=0.1 Vs control cases, § p= 0.01 Vs hepatitis cases, ‖ p< 0.001 controls and hepatitis cases.

SI: Serum iron. TIBC: Total iron binding capacity. TS: Transferrin saturation.

findings may be beneficial in interpretation of serum iron test results in patients with liver disease. However, persons with cirrhotic stage of liver disease associated with systemic iron overload were lacking in this study. Therefore, we cannot conclude definitely about values of serum iron parameters in such patients.

Previous comments regarding the necessity of liver biopsy for diagnosis of systemic iron overload in patients with CLD are doubtful due to some important factors: In some studies, hepatic iron accumulation associated with CLD was inappropriately regarded as iron overload (10). Some authors found elevated SI, ferritin or TS levels in nearly half of the chronic viral hepatitis cases (11,17). However, histological evaluations practically did not show hemochromatosis. Therefore, they suggested that in patients with chronic hepatitis in whom hereditary hemochromatosis is suspected, a liver biopsy should be performed. They did not state whether all of these parameters were simultaneously elevated in any patient. Additionally, they evaluated cirrhosis and chronic viral hepatitis cases together. Increased or high-normal values of SI (in chronic hepatitis), ferritin (in cirrhosis, predominantly in Class C) and TS (practically only in Class C cirrhosis) were also observed in our CLD patients. Simultaneously elevated ferritin and TS was confined to Class C cirrhotics. However, no single patient had elevation in all of these parameters. HFE-related hereditary hemochromatosis, which is practically absent in Turkey (18), is frequent in Europe and North America. This disorder was not mentioned between exclusion criteria in the above-mentioned studies. In the absence of molecular diagnostic tools, patients with additional hereditary hemochromatosis might have been included with chronic viral liver disease cases as a confounding factor. In the mentioned studies, hemochromatosis was diagnosed by iron determination in liver biopsy. It is quite clear that significant hepatic siderosis is not a prerequisite for hereditary hemochromatosis. Therefore, this criterion is not sufficient for discriminating hereditary hemochromatosis cases. It should also not be forgotten that SI level may be affected by food and transfusion.

In CLDs, a correlation between histological iron accumulation and fibrosis, which is the hallmark of hepatic cirrhosis, has been observed in many studies (19-24). These studies have been performed largely in hepatitis C patients. It was proposed that iron accumulation could trigger fibrosis (14,22,23). However, contrary findings have also been published (25,26). Congenital atransferrinemia is a rare disorder associated with hepatic siderosis (27). In this study, it was shown that as hepatic parenchymal failure progresses, TIBC (transferrin activity) decreases and consequently TS increases. This acquired hypotransferrinemia resulting in increased iron saturation of transferrin is likely the cause of hepatic siderosis in CLD. If this is the case, hepatic siderosis may be an indirect result instead of a cause of hepatic fibrosis. In accordance with this suggestion, TS was found to be the best predictor of the status of hepatic iron deposits in chronic hepatitis C (16). This hypothesis should be investigated in a study searching for correlations between hepatic iron deposition, TIBC (or transferrin level) and TS.

In conclusion, there is a good relationship between severity of parenchymal liver failure and aberrant serum iron test results. Patients with advanced cirrhosis frequently have increased TS (due to decreased TIBC) and ferritin levels. Patients with true systemic iron overload are characterized by hyperferremia in addition to increased TS and ferritin levels. These properties may be beneficial in the interpretation of serum iron test results in patients with liver disease.

This study has two main limitations. Although we intended to include similar numbers of cirrhotic patients (belonging to the 3 different Child-Pugh groups) and controls, Child-Pugh Class C cirrhotic cases were relatively overrepresented. This was mainly because we included sequential cirrhotic cases irrespective of their Child-Pugh classes. Secondly, we could only find 14 systemic iron-overloaded patients.

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