SERUM IRON PARAMETERS IN ALCOHOLIC CIRRHOSIS, CRYPTOGENIC CIRRHOSIS, CHRONIC HEPATITIS B AND CHRONIC HEPATITIS C

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ABSTRACT

BACKGROUND

Regular monitoring of serum iron parameters is helpful for assessing the severity of alcoholic liver disease. Assessment of serum iron parameters are used for screening hereditary haemochromatosis in chronic liver disease. Serum iron parameters in chronic liver disease have not been clearly described in most of the studies.

The aim of this study was to assess the serum iron, Total Iron Binding Capacity (TIBC), transferrin saturation and ferritin levels in common chronic liver disease like alcoholic cirrhosis, cryptogenic cirrhosis, chronic hepatitis C and chronic hepatitis B.

MATERIALS AND METHODS

110 consecutive patients with chronic liver disease admitted to the Gastroenterology Department, Government Medical College, Kozhikode were selected for the study. The categories of chronic liver disease included in our study were alcoholic cirrhosis (Group I, n = 40), cryptogenic cirrhosis (Group II, n = 30), chronic hepatitis C (Group III, n = 20) and chronic hepatitis B (Group IV, n = 20). Serum iron, ferritin, total iron binding capacity and transferrin saturation were estimated in the fasting sample.

Statistical Analysis- Analysis was performed using nonparametric Kruskal-Wallis and Bonferroni test to assess statistical significance of difference of continuous variables among and between groups, respectively. The results were considered statistically significant at the level of $p < 0.05$.

RESULTS

The serum iron level was normal and total iron binding capacity was low in all the four groups of chronic liver disease. Serum ferritin and transferrin saturation were significantly higher in alcoholic cirrhosis in comparison with cryptogenic cirrhosis and chronic hepatitis B, but was not statistically significant in comparison with chronic hepatitis C.

CONCLUSION

We observed irregularities in iron status in patients with alcoholic cirrhosis, cryptogenic cirrhosis, chronic hepatitis C and chronic hepatitis B.

KEYWORDS

Chronic Liver Disease (CLD), Serum Iron (SI), Total Iron Binding Capacity (TIBC), Transferrin Saturation, Cryptogenic Cirrhosis, Chronic Hepatitis B and Chronic Hepatitis C.

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BACKGROUND

Chronic liver disease is defined as a disease of the liver that involves progressive destruction and regeneration of the parenchyma leading to fibrosis and cirrhosis.[1] Several categories of chronic liver disease have been recognised.

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These include chronic viral hepatitis, alcoholic liver disease, metabolic chronic hepatitis, toxic chronic hepatitis, non-alcoholic steatohepatitis, autoimmune chronic hepatitis and cryptogenic cirrhosis.

Chronic hepatitis represents a series of liver dysfunction of varying causes for at least 6 months. In the United States, chronic hepatitis accounts for at least 50% of the cases of chronic liver disease and cirrhosis.[2] Chronic viral hepatitis is usually caused by hepatitis B and hepatitis C viruses. Hepatitis B and Hepatitis C are the underlying aetiological factors in most cases of hepatocellular carcinoma.[3,4] In the United States, Hepatitis C infection is the reason for 30 to 40 percentage of liver transplantation.

Cirrhosis of the liver is characterised by fibrosis and the conversion of normal liver architecture into a structurally

abnormal nodule that lack normal organisation. Viral hepatitis and alcoholism are the most common causes of cirrhosis.

Alcoholic liver disease comprises of alcoholic fatty liver, alcoholic hepatitis and alcoholic cirrhosis. In 80% of patients with severe alcoholic hepatitis, cirrhosis will coexist at presentation. The threshold for developing alcoholic liver disease is an intake of > 20 grams/day of alcohol for 10 years or more. The mortality of patients with alcoholic hepatitis with cirrhosis is 60% at 4 years.

Cryptogenic cirrhosis is the end stage of chronic liver disease in which its underlying aetiology remains unknown even after extensive clinical, serological and pathological evaluations.

Mild-to-moderate hyperbilirubinaemia accompanied by a modest rise in the levels of alanine aminotransferase and aspartate aminotransferase occur in chronic liver disease. Levels of alkaline phosphatase may be normal or marginally elevated. Viral markers are positive in viral hepatitis. Derangement in the hepatic synthetic function indicates more serious disease. Hypoalbuminaemia, prolongation of prothrombin time and coagulopathy are common in advanced liver injury. Ultrasonography is useful in detecting fatty and cirrhotic changes of the liver. Metabolic and autoimmune hepatitis is screened by the estimation of autoantibodies, alpha-1 antitrypsin, ceruloplasmin, serum copper and iron profile.

The liver plays an important role in iron homeostasis. Iron is stored as ferritin in the liver. The transport protein for iron, transferrin is produced in the liver.[5] Iron homeostasis is disturbed by hepatic injury and dysfunction of the liver. Excessive iron deposition in the liver leads to further injuries by triggering hepatocellular necrosis and fibrosis. The main target organ affected in hereditary hemochromatosis is liver.[6]

Serum Iron (SI), Total Iron Binding Capacity (TIBC), ferritin and transferrin saturation are the principal tests used in the assessment of iron overload. Serum iron parameters are usually abnormal in chronic liver disease.[7] Serum total iron binding capacity is usually decreased and ferritin is increased in many patients with chronic liver disease.[8] The serum ferritin values may predict hepatic iron deposition in chronic liver disease and severity of fibrosis.[9] There is well known iron status irregularities reported in alcoholic cirrhosis[10] and chronic viral hepatitis.[11] Regular monitoring of serum iron parameters is helpful for assessing the severity of alcoholic liver disease and to minimise the morbidity of liver injury.[12] Assessment of serum iron, total iron binding capacity, transferrin saturation and ferritin levels are used for screening hereditary hemochromatosis in chronic liver disease.[13] Serum iron parameters in chronic liver disease have not been clearly defined in most of the studies.[14] So this study was planned to assess serum iron parameters in common chronic liver disease.

AIM

To assess the serum iron, total iron binding capacity, percentage saturation and ferritin levels in patients with alcoholic cirrhosis, cryptogenic cirrhosis, chronic hepatitis C and chronic hepatitis B.

MATERIALS AND METHODS

110 consecutive patients with chronic liver disease admitted in the Gastroenterology Department, Government Medical College, Kozhikode were included in our study. The Institutional Ethical Committee approved the study and informed consent was taken. The descriptive study was conducted in the Biochemistry Department at Government Medical College, Kozhikode. Patients who were diagnosed to have chronic liver disease on the basis of history, clinical examination, viral marker study, serum liver function test, ultrasonography and gastroscopic examination were selected for the study. The categories of chronic liver disease included in our study were alcoholic cirrhosis (Group I, n = 40), cryptogenic cirrhosis (Group II, n = 30), chronic hepatitis C (Group III, n = 20) and cryptogenic hepatitis B (Group IV, n = 20). Those patients who failed to give a written consent and chronic liver disease due to aetiology other than alcoholic cirrhosis, viral hepatitis C, viral hepatitis B and cryptogenic cirrhosis were excluded from our study. Age, sex, socioeconomic status, education, religion and dietary habits were collected from all patients. The mode of presentation (jaundice, pallor, oedema, spider nevi and palmar erythema) was also recorded from all the patients with chronic liver disease.

Routine haemogram, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, albumin, prothrombin time, blood sugar, urea, creatinine and ultrasonography were done at the time of inclusion of patients into the study.

Fasting plasma samples for measurement of iron parameters were drawn from the selected 110 patients with chronic liver disease. Serum iron, total iron binding capacity, transferrin saturation and ferritin were estimated by the investigators in the Postgraduate Biochemistry Research Laboratory, Government Medical College, Kozhikode. Serum Iron (SI) and total iron binding capacity were tested in Transasia ERBA Chem-5 plus semiautomatic analyzer, Germany. Serum transferrin saturation was calculated by dividing serum iron by total iron binding capacity. Serum ferritin measurement was done by a particle-enhanced immunoturbidimetric method in the same machine.

Data Analysis

The Statistical Package for the Social Sciences (SPSS) for Windows software was used for statistical calculations. Analysis was performed using nonparametric Kruskal-Wallis and Bonferroni tests to assess significance of differences of continuous variables among and between groups, respectively. The results were considered statistically significant at the level of $p < 0.05$.

RESULTS

Mean age of the study subjects was 54.13 years with a range of 30 - 75 years; 69% (76) of the subjects were males. All patients with alcoholic cirrhosis were males and Hindus. The

majority of patients were from middle class family with primary education. Most of the patients were non-vegetarians. Table 1 depicts socio-demographic features of chronic liver disease.

Table 2 shows the baseline laboratory data of chronic liver disease. Hyperbilirubinaemia was seen in all types of liver disease. Transaminase values were either normal or mildly elevated and alkaline phosphatase was normal in all groups of chronic liver disease. Hypoalbuminaemia was seen in all types of chronic liver disease. Serum iron parameters obtained are presented in Table 3. Serum iron levels were normal and did not differ significantly among the analysed groups ($p = 0.078$). All groups of chronic liver disease had low serum total iron binding capacity value. Mean serum ferritin value in patients with alcoholic cirrhosis was 366 µg/dL and that in chronic hepatitis C was 323.9 µg/dL. Serum ferritin was significantly higher for patients with alcoholic cirrhosis in comparison with cryptogenic cirrhosis ($p = 0.001$) and chronic hepatitis B ($p = 0.003$), but was not statistically significant in comparison with chronic hepatitis C ($p = 0.770$). Transferrin saturation was significantly higher in alcoholic cirrhosis in comparison with cryptogenic cirrhosis ($p = 0.014$) and chronic hepatitis B ($p = 0.019$), but was not statistically significant in comparison with chronic hepatitis C ($p = 0.540$).

		Alcoholic Cirrhosis (N = 40)	**Cryptogenic Cirrhosis (N = 30)**	**Chronic Hepatitis C (N = 20)**	**Chronic Hepatitis B (N = 20)**
Age in years	Mean	52.60	56	57.65	49.95
	Range	34-70	33-75	34-75	30-75
Sex n (%)	Male	40 (100)	15 (50)	8 (40)	12 (60)
	Female	0 (0)	15 (50)	12 (60)	8 (40)
Socioeconomic Status n (%)	Poor	5 (12.5)	0 (0)	2 (10)	0 (0)
	Middle class	27 (67.5)	23 (76.7)	15 (75)	18 (90)
	Upper class	8 (20)	7 (23.3)	3 (15)	2 (10)
Education (%)	Illiterate	4 (10)	14 (46.7)	8 (40)	0 (0)
	Schooling	36 (90)	11 (36.7)	12 (60)	18 (90)
	Graduate	0 (0)	5 (16.6)	0 (0)	2 (10)
Religion n (%)	Hindu	40 (100)	11 (36.7)	10 (50)	8 (40)
	Christian	0 (0)	7 (23.3)	2 (10)	3 (15)
	Muslim	0 (0)	12 (40)	8 (40)	9 (45)
Diet n (%)	Vegetarian	8 (20)	9 (30)	3 (15)	1 (5)
	Non-Vegetarian	32 (80)	21 (70)	17 (85)	19 (95)

Table 1. Socio-Demographic Data in Chronic Liver Disease

	Alcoholic Cirrhosis (N = 40) (Mean ± SD)	**Cryptogenic Cirrhosis (N = 30) (Mean ± SD)**	**Chronic Hepatitis C (N = 20) (Mean ± SD)**	**Chronic Hepatitis B (N = 20) (Mean ± SD)**
Haemoglobin (g/dL) (14 - 16 g/dL)	8.67±3.28	8.21±2.98	9.06±4.35	8.26±3.64
FBS (mg/dL) (70 - 110 mg/dL)	78±36	78±26	78±24	105±35
Bilirubin (mg/dL) (0.2 - 1 mg/dL)	3.2±0.84	4.01±0.72	3.3±0.66	3.4±0.64
Conjugated Bilirubin (mg/dL) (0.1 - 0.4 mg/dL)	1.25±0.12	1.45±0.23	1.05±0.24	1.2±0.14
ALT (IU/L) (< 45 IU/L)	27.25±9.23	41.52±10.28	48.54±12.64	53.52±16.48
AST (IU/L) (< 35 IU/L)	49.5±13.48	34.5±16.33	28.5±10.44	45±13.45
ALP (IU/L) (40 - 125 IU/L)	99.21±45.44	96.51±53.22	81.58±46.47	99.54±37.49
Total protein (g/dL) (6 - 8 g/dL)	6.4±3.26	6.5±3.68	6.25±2.46	6.8±2.48
Albumin (g/dL) (3.5 - 5 g/dL)	2.7±0.74	3.1±0.69	2.31±0.54	2.8±0.48
Prothrombin Time (Seconds) (11 - 14 seconds)	21±7	17±4	16±5	19±6

Table 2. Mean Baseline Laboratory Data of Chronic Liver Disease

	Alcoholic Cirrhosis (N = 40) (Mean ± SD)	Cryptogenic Cirrhosis (N = 30) (Mean ± SD)	Chronic Hepatitis C (N = 20) (Mean ± SD)	Chronic Hepatitis B (N = 20) (Mean ± SD)
Iron (40 - 160 µg/dL)	68.4±26.32	43.16±28.27	75.11±32.41	51.66±22.31
TIBC (250 - 400 µg/dL)	199.35±31.24	223.54±38.28	217.54±40.57	248.88±46.38
Transferrin Saturation (20 - 33%)	39.22±5.68	21.15±7.87	37.36±4.69	22.61±6.98
Ferritin (20 - 300 µg/L)	366±42.85	77±30.57	323.9±52.38	92.88±25.92

Table 3: Mean Serum Iron Parameters in Chronic Liver Disease

DISCUSSION

We observed that serum iron parameters were aberrant in chronic liver disease. The mean serum iron concentration was normal in all the groups of chronic liver disease. Serum ferritin and transferrin saturation was higher in patients with alcoholic cirrhosis and chronic hepatitis C in our study. Previously, some authors also showed the association of abnormal serum iron tests with chronic liver disease. Krzysztof et al studied serum iron parameters among alcoholic and non-alcoholic chronic liver disease in Poland[15]; 136 patients with chronic liver disease were divided into five groups. The groups were chronic viral hepatitis C (Group I, n = 71), chronic viral hepatitis B (Group II, n = 29), alcoholic cirrhosis of the liver (Group III, n = 15), post-inflammatory cirrhosis of liver (Group IV, n = 13) and alcoholic hepatitis (Group V, n = 8). Their study also reported that the serum iron was normal in the patients with chronic liver disease (p = 0.098). The TIBC was lower in alcoholic cirrhosis in comparison with both chronic hepatitis C (p = 0.004) and chronic hepatitis B (p = 0.04). The transferrin saturation was statistically higher in alcoholic cirrhosis in comparison with chronic hepatitis C (p = 0.0031) and hepatitis B (p = 0.024). They concluded that all the chronic liver disease patients were associated with abnormalities in iron status. The most significant abnormality was seen in patients with alcoholic liver cirrhosis. We also observed similar results of iron parameters in alcoholic cirrhosis. The ferritin and transferrin saturation of alcoholic cirrhosis was not statistically significant in comparison with chronic hepatitis C in our study.

Tsung–Jung Lin et al conducted a study on serum iron status in patients with chronic hepatitis C and non-alcoholic fatty liver disease in Taiwan in 2005.[16] They observed that 34.48% of patients with chronic hepatitis C had elevated serum iron, ferritin and transferrin saturation. We observed high mean ferritin and transferrin saturation and normal mean serum iron levels in patients with chronic hepatitis C in our study.

Arber et al observed that serum iron, transferrin saturation and ferritin were increased in patients with chronic hepatitis C in comparison with hepatitis B or other non-viral, non-hemochromatotic liver diseases.[17] These results are undistinguished from our study.

Sikorska K et al conducted a study on disturbances of iron metabolism in chronic liver disease.[5] They concluded that serum iron parameters were altered in most of the patients with chronic hepatitis. The result of their study was comparable to our study.

Naciye Semnur B et al found that aberrant serum iron test results indicated a cirrhotic stage in chronic liver disease.[11] Patients with chronic hepatitis had normal serum iron parameters in their study. They observed statistically significant increase in ferritin and transferrin saturation in alcoholic cirrhosis when compared with chronic hepatitis. In our study, we observed high ferritin and transferrin saturation in alcoholic cirrhosis in comparison with chronic hepatitis B and cryptogenic cirrhosis. But serum iron, ferritin and transferrin saturation were normal in cryptogenic cirrhosis in our study. We had high ferritin and transferrin saturation in chronic hepatitis C in our study.

Hepatitis B virus-infected patients with cirrhosis had low serum iron binding capacity and high ferritin in comparison with non-cirrhotic hepatitis B virus and hepatitis C infected patients.[18]

Prieto J et al observed that higher ferritin was common in all patients with chronic liver disease. But most of the studies contradicted it. Ferritin level was high among alcoholic liver disease and chronic hepatitis C, but normal in patients with chronic hepatitis B and cryptogenic cirrhosis.[19]

Bell H et al reported that serum ferritin was increased in all patients with hemochromatosis and 58% of chronic alcoholic liver disease and 22% of chronic non-alcoholic liver disease.[20] Serum ferritin is more frequently elevated in alcoholic cirrhosis in comparison with other liver disease in their study. We also observed high ferritin level in alcoholic liver disease in our study.

The factors that affect the excess iron stores in alcoholic cirrhosis and chronic hepatitis C have not been fully characterised. Increased liver iron stores may be due to alcohol abuse and hepatitis virus C infection. Excessive iron deposition in the liver leads to further progression of chronic hepatitis C infection and alcoholic disease and in turn may alter iron homeostasis.[21] Persons abusing alcohol may have increased depositions of iron in the liver due to the influence of ethanol on the increased absorption of iron from the gut.[22]

CONCLUSION

We concluded that the iron parameters are deranged in chronic liver disease. The serum iron was normal in patients with alcoholic cirrhosis, chronic hepatitis B, chronic hepatitis C and cryptogenic cirrhosis. Serum total iron binding capacity was low in all the groups of chronic liver disease

studied by us. Alcoholic cirrhosis and chronic hepatitis C patients had high serum ferritin and transferrin saturation levels. Serum ferritin and transferrin saturation were normal in patients with chronic hepatitis B and cryptogenic cirrhosis.

Limitations of Study

We have not included control groups in our study. We used standard reference values for comparison.

REFERENCES

1. Asharf S, Neem S. Frequency of hypersplenism in chronic liver disease patients presenting with pancytopenia. Special Edition Annals 2010;16(1):108-110.
2. Beaumont C, Vaulont S. Iron homeostasis. In: Beaumont C, Beris P, Beuzard Y, et al, eds. The handbook- Disorders of iron homeostasis, erythrocytes, erythropoiesis. European School of Haematology 2006:392-406.
3. Batts KP. Iron overloads syndromes and the liver. Mod Pathol 2007;20(Suppl 1):S31-39.
4. Wallach J. Interpretation of diagnostic tests. 6th edn. Boston: Little, Brown and Company 1996.
5. Sikorska K, Stalke P, Lakomy EA. Disturbance of iron metabolism in chronic liver diseases. Med Sci Monit 2003;9(Suppl 3):64-67.
6. Metwally MA, Zein CO, Zein NN. Clinical significance of hepatic iron deposition and serum iron values in patients with chronic hepatitis C infection. Am J Gatroentrol 2004;99(2):288-291
7. Fletcher LM, Halliday JW, Powell LW. Interrelationships of alcohol and iron in liver diseases with particular reference to the iron-binding proteins, ferritin and transferrin. J Gastroenterol Hepatol 1999;14(3):202-214.
8. DI Bisceglie AM, Axiotics CA, Hoofnagle JH, et al. Measurements of iron status in patients with chronic hepatitis. Gastroenterology 1992;102(6):2108-2113.
9. Khare S, Garg VK, jatav O. Serum iron and TIBC parameters in chronic liver disease. Sch J App Med Sci 2015;3(5e):2128-2131.
10. Phatak PD, Sham RL, Raubertas RF. Prevalence of hereditary hemochromatosis in 16031 primary care patients. Ann Intern Med 1998;129(11):954-961.
11. Büyükaşik NS, Nadır I, Akin FE, et al. Serum iron parameters in cirrhosis and chronic hepatitis: detailed description. Turk J Gastroenterol 2011;22(6):606-611.
12. Ascher NL, Lake JR, Emond J, et al. Liver transplantation for hepatitis C virus-related cirrhosis. Hepatology 1994;20(1 pt 2):24S-27S.
13. Di Biscegie AM, Rustogi VK, Hoofnagle JH, et al. Hepatocellular carcinoma. Ann intern Med 1998;108:390-401.
14. Alter MJ. Epidemiology of hepatitis C in the west. Semin Liver Dis 1995;15(1):5-14.
15. Jurczyk K, Wawrzynowicz-Syczewska M, Boroń-Kaczmarska A, et al. Serum iron parameters in patients with alcoholic and chronic cirrhosis and hepatitis. Med Sci Monit 2001;7(5):962-965.
16. Lin TJ, Lin CL, Wang CS, et al. Prevalence of HFE mutations and relation to serum iron status in patients with chronic hepatitis with nonalcoholic fatty liver disease in Taiwan. World J Gastroenterol 2005;11(25):3905-3908.
17. Arber N, Konikoff FM, Moshkowitz M, et al. Increased serum iron and iron saturation without liver iron accumulation distinguish chronic hepatitis C from other chronic liver diseases. Dig Dis Sci 1994;39(12):2656-2659.
18. Mao W, Hu Y, Lou Y, et al. Abnormal serum iron markers in chronic hepatitis B virus infection may be because of liver injury. Eur J Gastroenterol Hepatol 2015;27(2):130-136.
19. Prieto J, Barry M, Sherlock S. Serum ferritin in patients with iron overload and with acute and chronic liver diseases. Gastroenterology 1975;68(3):525-533.
20. Bell H, Skinningsurd A, Raknerud N, et al. Serum ferritin and transferrin saturation in patients with chronic alcoholic and non-alcoholic liver diseases. J Intern Med 1894;236(3):315-322.
21. Nelson JE. Iron and hepatitis C. Current Hepatitis Reports 2004;3:140-147.
22. Whitfield JB, Zhu G, Heath AC, et al. Effects of alcohol consumption on indices of iron stores and iron stores on alcohol intake markers. Alcohol Clin Exp Res 2001;25(7):1037-1045.