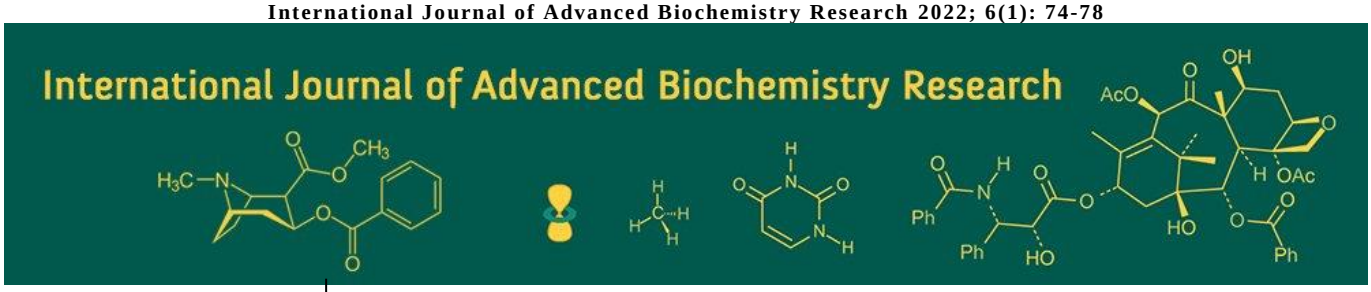

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Study of serum iron parameters in chronic liver disease

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Abstract
Background: Liver is a complex organ, essential for iron metabolism in the body and is recognised as the primary site for the synthesis of iron-related plasma proteins. Liver also regulates iron concentrations in an effective manner and identifies changes in systemic iron requirements. Haematological abnormalities are often associated with chronic liver diseases. Raised iron stores show high response to the infection of hepatitis C, resistance to interferon, therapy & development of CLDs.
Objective: This study intends to assess the association of iron parameters with liver enzymes in patients of CLD and to compare these parameters with healthy controls.
Materials and Methods: This study was carried out from January to December 2021 in the Department of Biochemistry, Teerthanker Mahaveer Hospital. A total of 100 individuals, out of which 50 were chronic liver disease patients and 50 as healthy controls were selected. Serum iron parameters were measured using an automated method.
Results: Findings of this study reveals that serum iron and serum transferrin saturation levels were significantly increased (p<0.001), while serum UIBC and TIBC levels were significantly decreased (p<0.001) when compared with healthy controls.
Conclusion: Based on our data we demonstrate that these findings will provide a fair framework for the prognosis of liver diseases and are also likely to be informative for reducing the risk of complications associated with liver diseases.

Keywords: Chronic liver disease, iron, TIBC, transferrin saturation and UIBC

Introduction
The liver is the body's largest solid organ, weighing 1-1.5 kg and accounting for 1.2-2.5% of total body weight. Hepatocytes are the most numerous cells in the liver, accounting for two-thirds of its mass and play crucial role in maintaining homeostasis and health [1].
The liver is responsible for over 5000 biological processes, including clotting blood, resisting infections and disease, repairing after injury and controlling metabolite metabolism such as cholesterol, glucose, iron and many others. A range of factors that harm the liver can produce liver illnesses, which can be hereditary or caused by a variety of circumstances. In truth, there are many different types of liver disease that can be caused by a virus, drug or chemical damage, obesity, diabetes or an immune system attack [2]. Chronic liver disease is a type of severe liver condition marked by the damage, failure and regeneration of the liver parenchyma, eventually leading to fibrosis and cirrhosis [3].
Cirrhosis is the last stage of chronic liver disease, characterised by disturbance of the liver's architecture, the development of large nodules, vascular reorganisation, neo-angiogenesis and the deposition of an extracellular matrix. The focus is on the common etiologies, clinical symptoms and therapy of chronic liver disorders, which is an extraordinarily common clinical condition. Toxins, long-term alcohol misuse, infection, autoimmune disease, genetic and metabolic disorders are just a few of the etiologies for chronic liver disease.

Etiology
The following are the most common etiologies
- **Alcoholic liver disease:** It includes alcoholic fatty liver with or without hepatitis, alcohol hepatitis (reversible because of acute ingestion) to cirrhosis (irreversible) [4].
- **Non-alcoholic Fatty liver disease (NAFLD/NASH):** It covers a wide range of conditions, including non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis

(NASH), fibrosis and cirrhosis. With increased levels of type 2 diabetes and metabolic syndrome, it is becoming more common [5].

- **Chronic viral hepatitis:** Viral hepatitis, which causes chronic hepatitis B, C and D, cirrhosis and decompensated illness, liver cancer and extrahepatic manifestations, greatly contributes to the burden of liver disease [6].

Genetic causes

a. Alpha 1 antitrypsin deficiency
b. Hereditary hemochromatosis
c. Wilson's disease

- **Autoimmune causes:** Primary biliary cirrhosis (PBC), Primary Sclerosing Cholangitis (PSC) and Autoimmune Hepatitis (AIH) [4].

CLD accounts for major morbidity and mortality around the world. Alcoholic liver disease, chronic viral hepatitis, including hepatitis B and C, non-alcoholic fatty liver disease and hemochromatosis are the most common forms of CLD in the developed world [7].

Patients with CLD develop hepatic dysfunction and portal hypertension, which leads to liver-related morbidity and mortality [4]. There is some degree of iron overload found in patients suffering from chronic liver disease between 10-30%. However, it is known that iron can accumulate in the liver due to liver damage [8].

Moreover, besides various functions it performs, liver is an important organ for iron homeostasis. It also makes transferrin and hepcidin, which are iron transport protein in the blood and hormone that regulate iron metabolism respectively [9].

The liver is the primary site for the generation of proteins that keep systemic iron balance in check, as well as a storage place for excess iron. It also aids in the mobilisation of iron from hepatocytes to circulation in order to meet the body's metabolic needs. The accumulation of iron in the liver, on the other hand, may trigger a radical reaction that damages the liver cells. As a result, liver problems may disrupt iron homeostasis [10].

Hepcidin is a 25-amino acid peptide liver hormone that regulates the amount of iron released into the blood plasma, and is produced by hepatocytes which are known to be the major cell types in the liver [11, 12].

One characteristic of the iron-liver link is that, the liver is one of the main targets in hemochromatosis [13]. Hereditary hemochromatosis is one of the autosomal-recessive genetic disorder that is known as a major cause of iron overload [14].

The total iron binding capacity (TIBC) and serum iron (SI) are crucial assays for determining iron disorders. Transferrin saturation is another commonly utilised metric (TS) [15].

For liver diseases, testing and understanding serum iron parameters is critical for a variety of reasons:

1. Serum transferrin saturation (TS) levels are used for screening of hereditary hemochromatosis [15].
2. As based on evidences from few studies iron may also be important for progression of liver fibrosis in viral hepatitis [16].
3. Increased serum levels of iron and transferrin saturation are reported in non-alcoholic fatty liver disease and fatty liver disease, chronic hepatitis C and liver cirrhosis [17].

However, the effect of severity of iron parameters on liver disease has not been clearly defined in any study.

There remain open questions regarding the clinical significance of serum parameters of iron metabolism in various chronic liver diseases and there were variable results.

Therefore, this study will be directed to estimate serum iron parameters (serum iron, serum TIBC, serum UIBC) levels in chronic liver disease patients.

Materials and Methods

The study was done in the Department of Biochemistry, Teerthanker Mahaveer College & Research Center General Medicine OPD in Moradabad, Uttar Pradesh from January 2021 to December 2021. A total of 100 subjects under the age limit 20-60 years [18] were selected and categorized into two classes. 50 diagnosed cases of chronic liver disease (alcoholic liver disease, non-alcoholic fatty liver disease, liver cirrhosis, chronic viral hepatitis) recruited for this study, were included in class I, while, class II included 50 apparently healthy individuals age and sex matched. This is a cross-sectional study that involved chronic liver disease patients at the outpatient department of TMMC & RC.

Signed consent forms were obtained from all applicants, regardless of gender or clinical stage of the disease.

Clean venepuncture was used to collect approximately 5ml blood samples from the antecubital fossa into plain test tubes that had already been labelled with no undue pressure on either the arm or plunger of the syringe. After allowing blood samples to coagulate, they were kept for centrifugation at 3000 RPM for 5 minutes to obtain sera. The clear sera were separated and transferred to sterile bottles for enzyme assay. When not in use right away, they were stored at 20 °C and used within 5 days.

Exclusion criteria

Malignancy, pregnancy, chronic renal failure, drugs affecting iron metabolism such as glucocorticoid, synthetic estrogens, aspirin, tamoxifen, methotrexate or any other disease which affect serum iron level were excluded from the study [19].

Various methods were used

- Serum iron parameters (serum iron, serum TIBC, serum UIBC) were estimated by the Ferrozine method [20].
- Serum TIBC = UIBC + Serum iron.
- The value of percent TS was estimated by: Serum iron capacity/iron-binding capacity× 100 [21].
- ALT and AST by IFCC method [22].
- ALP and GGT by Kinetic method [23, 24].
- Total bilirubin and direct bilirubin by Diazo method [25].

Statistical analysis

The statistical calculation was carried out using the latest version of statistical software named SPSS 28.0 for the assessment of data. Microsoft Word and Excel were used to generate graphs.

Significant value is evaluated as a p-value of less than 0.05 and a highly significant is described as a p-value of less than 0.001.

Results

The results of the measured different biochemical parameters in the research were listed below for hypothyroid patients and healthy subjects.

Table 1: Distribution of age group between control group and cases

Age (years)	20-30	31-40	41-50	51-60
Cases	15	11	14	10
%	30	22	28	20
Controls	13	16	15	6
%	26	32	30	12

Table 2: Comparison of percentage of gender between control group and cases

Parameter	Control group (n = 50)		Patients suffering from chronic liver disease (n = 50)	
Gender	Male	Female	Male	Female
No of Individuals	21	29	30	20
Percentage	42%	58%	60%	40%

Table 3: Comparison of Mean and SD values of various measured parameters between chronic liver disease patients and healthy controls:

Parameters measured	Controls (n= 50)	Cases (n= 50)	p-value
Age (years)	37.84±9.40	39.74±11.84	> 0.05
Total bilirubin (mg/dl)	0.846±0.244	7.827±3.576	<0.001
Direct bilirubin (mg/dl)	0.44±0.16	3.392±1.706	<0.001
Indirect bilirubin (mg/dl)	0.418±0.127	4.526±2.167	<0.001
SGOT (IU/L)	33.18±4.50	124.3±41.06	<0.001
SGPT (IU/L)	32.2±4.65	131.8±35.08	<0.001
ALP (U/L)	89.3±17.84	175.3±41.65	<0.001
GGT (U/L)	32.40±13.17	92.44±33.28	<0.001

The mean±SD levels of liver profile (total, direct, indirect, ALT, AST, ALP and GGT) in patients with chronic liver disease were higher as compared to mean±SD of controls. (Thus, the above result shows that the cases and controls have been selected appropriately).

Table 4: Mean and SD of serum iron, serum UIBC, serum TIBC and transferrin saturation levels between cases and controls were compared.

Iron Parameters	Control Mean±SD (n= 50)	Patients Mean±SD (n= 50)	p-value
Iron (µg/dl)	89.26±33.43	154.15±37.68	<0.001
TIBC (µg/dl)	313.74±38.76	231.90±58.19	< 0.001
UIBC(µg/dl)	224.48±38.67	80.41±72.55	<0.001
Transferrin saturation (%)	28.39±0.098	69.35±0.194	<0.001

The activity of serum iron in patients with chronic liver disease was more in cases than in healthy controls. However, the mean value of serum TIBC declined in chronic liver disease cases in comparison to healthy subjects. The analysis depicts that the mean value of serum UIBC was slightly decreased in cases as compared to healthy individuals but the difference was not significant. Also, Comparable values of serum transferrin saturation were obtained for control group and cases group and were statistically highly significant (p<0.001).

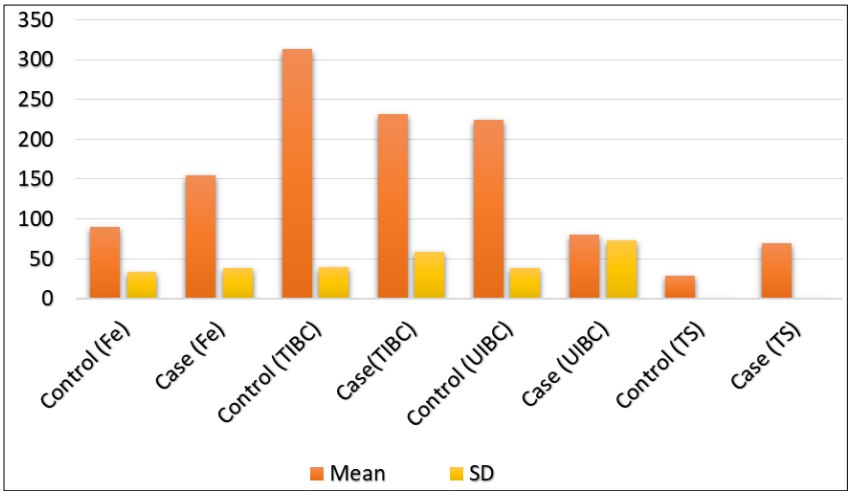

Fig 1: Shows muscle serum iron parameters in cases and controls

Discussion

In the human body, liver is a vital organ, which is in charge of various functions, including metabolism, immunity, digestion, detoxification, and vitamin storage, among others [26]. It serves as a centre for nutrient metabolism and waste metabolite excretion [27].

Chronic liver disease is identified by an ongoing process of inflammation, injury & reformation of the liver cells, that results in fibrosis and cirrhosis [4]. Haematological abnormalities are often associated with CLDs. The liver is an important organ in maintaining iron homeostasis [28]. A complete loss of liver function could result in death in minutes, demonstrating the liver's importance [29].

The present study was conducted on patients already diagnosed with chronic liver disease to examine the association between serum markers of iron metabolism (serum iron, serum TIBC, Serum UIBC and serum percentage transferrin saturation) and liver enzymes in patients of CLD and compare these parameters with healthy controls.

Our study showed a higher prevalence of chronic liver disease for males as compared to females. There was a total of 60% male persons with CLD. Also, the study showed predominant results of CLD in cirrhosis and chronic hepatitis. The study was conducted on male and female patients already diagnosed with chronic liver disease under 20-60 years of age. This is a cross-sectional study with a total of 100 individuals out of which 50 were already diagnosed with CLD and 50 healthy controls were selected.

The present research shows a significant rise in serum iron and TS levels. However, serum TIBC value was decreased in patients of CLD as compared to controls. It also depicts a significant increase in the concentration of liver enzymes, serum AST, serum ALT, serum ALP and serum GGT, serum TB, DB and INB in cases as compared to that of normal individuals.

Table 4 shows the comparison of serum iron, serum TIBC, serum UIBC and % transferrin saturation (TS) levels respectively between cases and controls. We found a significant rise in mean values of serum iron (154.15±37.68) with a p-value of < 0.001 in the case of chronic liver disease patients as compared to healthy individuals (89.26±33.43). TS levels also showed a significant increase in CLD patients (69.35±0.194) when compared with controls (28.39±0.098) with a p-value < 0.001. While we found a significant decrease in values of serum TIBC in chronic liver disease patients (231.90±58.19) when compared with controls (313.74±38.76) with a p-value of < 0.001. Serum UIBC levels were also decreased in CLD patients with a mean of 80.41±72.55 when compared with healthy controls (224.48±38.67). Similar results were obtained in a study conducted by Radicheva *et al*., 2018 [30] they showed the elevations in levels of Fe and transferrin saturation in various levels of CLD. According to them serum iron and transferrin saturation were elevated in cases of alcoholic liver disease, NAFLD and Chronic hepatitis C when compared with healthy controls.

Same findings were reported by Ibrahim NL in which they measured the concentration of trace elements in children with CLD and their association with liver profile. They found that serum iron (Fe) and transferrin saturation (TS) were significantly higher in CLD's than in control group whereas, TIBC was significantly lower in the cases as compared to control group [31].

Similarly, Ali H *et al*., 2011 [32] found in their study that serum iron was increased in 16.7% of fatty liver subject versus 7.4% of normal liver subjects.

The findings of the current study were in agreement with the results of Raouf *et al*. 2013 [33] They reported significantly higher serum Fe and transferrin saturation in cases than healthy subjects, while their findings reveal significantly low TIBC in patients of chronic liver disease as compared to healthy subjects.

Again, the findings of our study go in accordance with the study of H Al Baldawi D *et al*., 2017 [34] in which they found that serum TIBC was lower in patients of chronic liver disease than in control group whereas, serum iron was increased in cases than the healthy controls.

And according to the study done by Khare S *et al*., 2015 [21] serum iron increased and TIBC decreased with increasing disease severity.

Buyukasik *et al*., 2011 [35] stated aberrant serum iron levels in cirrhosis and increased transferrin saturation levels and decreased TIBC levels.

Table 3 shows the comparison of serum TB, DB and INB, serum ALT, AST, ALP and GGT in cases and controls respectively.

The current study suggests a markedly significant increase in serum total bilirubin, direct bilirubin, indirect bilirubin serum ALT, serum AST, serum ALP and serum GGT.

On comparing the mean values using the student's t-test, serum TB, DB and INB were found to be (7.872±3.576), (3.392±1.706), (4.526±2.167) in chronic liver disease cases and were significantly increased (p<0.001) than that of controls (0.846±0.244), (0.44±0.16), (0.418±0.127) respectively. Similarly, the mean values of serum SGPT, serum SGOT, serum ALP and serum GGT were found to be (124.3±41.06), (131.8±35.08), (175.3±41.65) and (92.44±33.28) respectively in CLD patients and were significantly higher when compared with controls and were found to be (33.18±4.50), (32.2±4.65), (89.3±17.84) and (32.40±13.17).

These findings of the present study correspond with the results of Raouf *et al*. 2011 [32] According to them the levels of liver enzymes (SGPT, SGOT, ALP, GGT) total bilirubin and direct bilirubin were high significance in the CLD group than normal individuals.

Ibrahim NL also found significantly higher levels of SGOT, SGPT, ALP, GGT, total and direct bilirubin in the CLD's than the control group [31].

A study by Yoo *et al*. 2019 [36] stated that liver cirrhotic group showed slightly but significantly higher levels of AST, ALT and gamma-glutamyl transferase (GGT) than the control group.

Conclusion

From the findings of the current study, we concluded that there is a difference in every serum marker of iron metabolism in comparison with healthy individuals. Serum iron and TS levels were elevated and were significantly raised in subjects with chronic liver illness in comparison to healthy subjects, and revealed a highly significant positive association with serum markers of liver profile. Serum TIBC and UIBC levels were significantly decreased in CLD patients as compared to that of healthy subjects and displayed a highly significant negative correlation with liver profile.

Chronic liver illness impairs the liver's synthetic processes, such as the generation of hepcidin, an important protein in iron metabolism. Patients with CLDs have a tendency to develop an abnormally high amount of Fe in their liver parenchyma due to lower levels of hepcidin, which causes iron to deposit in the liver and greater values of non-transferrin-bound iron in bloodstream. Raised Fe stores to result in a high response to infection of hepatitis C, resistance to interferon, therapy & development of CLDs.
Serum TIBC level may be changed in chronic liver disease. TIBC levels depend on transferrin which is produced in liver. In CLD there is reduced synthesis of transferrin, thereby, TIBC progressively decreases with disease severity. So there is a good association between the course of chronic liver illness and altered levels of serum markers of iron metabolism i.e., serum iron, TIBC, UIBC and transferrin saturation. Thus, we concluded that assessment of iron parameters in CLD patients can be used to find out iron homeostasis and predicting the occurrence of complications and can govern the prognosis of patients with liver disease for better patient supervision and also to lessen the morbidity and mortality associated with liver injury.

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Conflict of Interest: No conflict of interest was declared.

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