Assessment of serum iron markers and hepcidin in patients with chronic hepatitis B and C viruses

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Abstract: Background: Patients with hepatitis C (HC) and B (HB) often have elevated serum iron markers, which may worsen liver injury. **The aim of** this study was to evaluate serum iron markers and serum hepcidin levels in patients with chronic hepatitis (B & C) viruses. The study was conducted on 40 patients with chronic hepatitis (B & C) viruses in addition to 15 as a control group from Menoufia University and National Liver Institute. **Results**: There was no significant difference between the three studied groups regarding demographic data which include, age, BMI and sex, the three groups was matched regarding demographic data. Regarding liver function tests, serum albumin and total bilirubin show insignificant difference between the three studied groups, while direct bilirubin shows a significant increase in both HBV and HCV patients more than the control group. Both AST and ALT show a significant increase in both HBV and HCV patients than the control group, INR show insignificant difference between the three studied groups. Regarding iron items, serum iron in the three studied groups show insignificant difference, while serum ferritin show a significant increase in HBV group than the control and HCV, serum transferrin show a significant increase in HCV group more than the other two groups, on the other hand, it was found significant increase in serum transferrin in HBV more than the control group. hepcidin show a significant increase in both HBV and HCV group than the control, also there was a significant increase in serum hepcidin in HCV group more than the HBV.

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1. Introduction

Iron (ferrum in Latin) with an atomic number of 26, is the most common element on Earth. It is essential in most living organisms. Iron binds to cofactors in hemes, myoglobin, cytochrome P450, and catalases **(1).**

Iron homeostasis in the human body is maintained by mechanisms controlling iron absorption from the intestinal tract, iron recycling from macrophages and mobilization of hepatic iron stores. **(2)**.

Hepcidin, a recently discovered low-molecular 25 amino acid (cysteine-rich) hepatic peptide plays an important role in iron metabolism **(3).**

Hepcidin and its interaction with the Trans membrane iron transporter ferroportin (FPN) play crucial roles in the systemic iron balance through down-regulation of iron release from enterocytes and phagocytes. The expression of hepcidin is a complex process, strongly inhibited by hypoxia, anemia and iron deficiency while being activated by inflammation and iron overload. **(4).**

Production of hepcidin is regulated by iron and additionally by the erythropoietic requirement for iron **(5).**

It was found that hepcidin deficiency is associated with iron overload while overexpression of hepcidin is associated with a severe and often fatal iron-deficiency, which is consistent with the hypothesis that hepcidin is a negative regulator of body iron **(6).**

This role has been confirmed in a number of studies which focused mainly on hepcidin acting as a systemic iron-regulatory hormone**, (7)** through inhibition of intestinal absorption**,** macrophage release as well as regulation of the placental passageof iron **(8).**

Data from different studies showed a decrease in serum hepcidin in non-alcoholic fatty disease, alcohol liver disease, and chronic hepatitis C compared to healthy subjects and other chronic liver disease associated with chronic hepatitis or autoimmune pathogenesis. **(9).**

Furthermore, more advanced hepatic fibrosis is associated with decreased serum hepcidin level, indicating that hepcidin might serve as a potential biomarker for fibrosis and cirrhosis **(10).**

Many experimental and clinical studies suggest that chronic iron deposition promotes the progression of liver damage and increases the risk of fibrosis,

cirrhosis, and hepatocellular carcinoma in chronic hepatitis C patients (**11 & 12**).

Furthermore, some studies suggest that excess iron in the liver may induce adverse effects on patients' response to antiviral therapy for chronic hepatitis C **(13 & 14).**

Data on the prevalence and clinical significance of disturbed iron metabolism in patients with HBV-related cirrhosis are still lacking. It remains unclear whether altered serum iron markers observed in HBV infection are related to HBV infection or to liver injury that is associated with chronic HBV infection. **(15).**

The aim of this study was to evaluate serum iron markers and serum hepcidin levels in patients with chronic hepatitis B and C viruses.

2. Subjects and Methods

Subjects:

The study was conducted on 40 patients with chronic hepatitis (B & C) viruses in addition to 15 as a control group from Menoufia University and National Liver Institute in the period from October to November 2016. An informed consent was obtained from all patients.

Inclusion criteria:

- Patients with chronic HBV infection who are with positive HCV antibody for more than 6 months.
- Patients with chronic HCV infection who are with positive HBs Ag for more than 6 months.

Exclusion criteria:

- Known metabolic liver disease.
- Hepatic & extra hepatic Malignancies.
- Anemia (HB concentration < 13 g/dl in males and 12 g/dl in females).
- Patients receive blood transfusion.
- Treatment of anemia with iron in last 6 months.
- Patients with chronic kidney diseases.

Methods:

- Full History Taking including age, sex, and presence of chronic liver disease.
- Personal history.
- Family history.
- Drug history.
- History of other co morbidities (e.g.DM, HTN).
- Complete clinical examination:
- General examination.
- Abdominal examination for organomegaly.
- Laboratory Investigations Including:

A -Hematological testes:

- C.B.C.
- International Normalization ratio (INR).

B -Biochemical testes:

- Liver function testes including (Serum albumin, total and direct serum bilirubin, alanine transaminase (ALT) and aspartate transaminase (AST) levels and serum AFP).
- Serum iron markers (iron, ferritin and transferrin).
- Serum hepcidin level.
- Serum HBe Ag level.
- Measurement of FIB4.

C- Polymerase chain reaction (PCR) assay:

For patients with chronic hepatitis B and C.

D-Radiological investigations including:

- Abdominal ultrasonography for all cases.

Sample collection:

Blood samples were collected from each participant by venipuncture in Empty centrifuge tubes: incubated in water bath at 37^0C for 15 minutes then centrifuged at 3500 rpm. Sera were separated, divided into aliquots and stored at – 80^0C till use. Haemolysed samples were discarded.

3. Results

Table (1), show the demographic data of the studied patients group, it was found that there was no significant difference between the three studied groups regarding demographic data which include, age, BMI and sex. i.e. the three groups was matched regarding demographic data.

Table (2), shows the clinical data of the studied patients group, it was found that there was 4 cases (21.1%) in HCV patients was hypertension, there was a significant increase in HCV in the number of hypertension patients in relation to other two groups. In HBV patients 3 cases was +ve HB e Ag.

Table (3), shows the comparison between the three studied groups regarding liver function tests, serum albumin and total bilirubin show insignificant difference between the three studied groups, while direct bilirubin show a significant increase in both HBV ad HCV patients more than the control group. Both AST and ALT show a significant increase in both HBV and HCV patients than the control group, INR show insignificant difference between the three studied groups. Fib4 show a significant increase in HCV more than HBV group. PCR show a significant increase in HCV patients more than HBV group.

Table (4), shows the comparison between the three studied groups regarding iron items, serum iron in the three studied groups show insignificant difference, while serum ferritin show a significant increase in HBV group than the control and HCV, serum transferrin show a significant increase in HCV group more than the other two groups, on the other hand, it was found that there was a significant increase HBV more than the control group. Hepcidin show a significant increase in both HBV and HCV group than the control, also there was a significant increase in HCV group more than the HBV.

Table (5), shows the comparison between the three studied groups regarding PV diameter, Caudate span, Spleen span, and fibroscan (number). PV diameter shows a significant increase in HCV group than the control and HBV group. Caudate span show a significant decrease in HCV patients less than control ad HBV group. The fibroscan (number) in the two patients groups show insignificant difference.

Table (1): Demographic data of the studied patients group.

	Control (N=15)		**HBV patients (N=20)**		**HCV patients (N=20)**		**Test**	**P**
Age								
Range (years)	22.0-58.0		20.0-55.0		27.0-70.0			
Mean	41.8		36.25		47.2		ANOVA	0.069(NS)
S.D.	12.1		10.82		13.11		3.65	
BMI								
Range	21.0-36.8		21-40.0		20.1-40.8		ANOVA	0.107(NS)
Mean	24.9		29.2		28.5			
S.D.	2.01		4.98		5.11		2.68	
Gender	No	%						
Male	7	46.7	11	55.0	10	50.0	X^2	0.80(NS)
Female	8	53.3	9	45.0	10	50.0	0.44	

BMI= (Body mass indices) – No= Number – SD= stander deviation – %=Percentage- NS= Non significant (P-value> 0.05) - X2= `Chi square test

Table (2): Clinical data of the studied patients group.

	Control (N=15)		**HBV patients (N=20)**		**HCV patients (N=20)**		**Test**	**P**
	No.	%	No.	%	No.	%		
DM	0	0.0	0	0.0	0	0.0	-	-
HTN	0	0.0	0	0.0	4	21.1	7.96	0.019*(S)
HB e Ag+ve	0	0.0	3	15.0	0	0.0	2.33	0.069(NS)
HCV Ab+ve	0	0.0	0	0.0	0	0.0	-	-

No= Number – %=Percentage- NS= Non significant (P-value> 0.05) – HTN= elevation of Systolic blood pressure > 140 and Diastolic blood pressure >90 – DM= Fasting blood sugar more than > 126 Mg/dl – S= significant (≤0.05%)

Table (3): Comparison between the three studied groups regarding liver function tests.

	Control (N=15)	**HBV patients (N=20)**	**HCV patients (N=20)**	**Test**	**P**
S. albumin					
Range	3.5-5.5	3.5-5.2	3.4-4.8	1.920	0.157(NS)
Mean	4.45	4.22	4.08		
S.D.	0.73	0.45	0.43		
T. bilirubin					
Range	0.2-1.0	0.2-1.0	0.3-1.1	0.097	0.908(NS)
Mean	0.66	0.65	0.68		
S.D.	0.30	0.24	0.21		
D. bilirubin					
Range	0.0-0.2	0.1-0.3	0.1-0.4	5.619	0.006*(S)
Mean	0.12	0.18	0.20		
S.D.	0.07	0.05	0.08		
A.S.T					
Range	17.0-39.0	15.0-84.0	21.0-120.0	4.971	0.011*(S)
Mean	26.47	34.00	46.26		
S.D.	6.72	17.31	25.09		
A.L.T					
Range	16.0-36.0	13.0-112.0	12.0-125.0	5.039	0.010*(S)
Mean	23.20	41.90	46.95		
S.D.	6.52	27.38	24.67		
I.N.R	1.1-1.1	1.0-1.2	1.0-1.6	1.168	0.319(NS)
Range	1.10	1.07	1.12		
Mean	0.00	0.06	0.15		

	Control (N=15)	HBV patients (N=20)	HCV patients (N=20)	Test	P
S.D.					
Fib4					
Range	-	0.3-2.2	0.5-6.8	7.206	0.011*(S)
Mean	-	0.95	1.94		
S.D.	-	0.12	0.36		
PCR					
Range	-	160.0-300000.0	15700.0-11100000.0	6.697	0.014*(S)
Mean	-	25287.00	1591145.57		
S.D.	-	15464.08	621007.68		

S= serum – T= total - D= direct – A.S.T= Aspartate transaminase – A.L.T= Alanine transaminase- I.N.R=international normalized ratio - NS= Non significant (P-value> 0.05)- PCR= polymerase chain reaction

Table (4): Comparison between the three studied groups regarding iron Parameters.

	Control (N=15)	HBV patients (N=20)	HCV patients (N=20)	Test	P
S. Iron					
Range	26.5-61.5	32.7-260.0	38.9-136.2	2.482	0.094(NS)
Mean	43.52	67.17	66.08		
S.D.	9.07	48.70	27.25		
S. ferritin					
Range	17.0-35.0	24.0-85.0	14.0-52.0	27.737	0.001*(S)
Mean	23.67	45.90	22.84		
S.D.	5.02	14.81	8.96		
S. transferrin					
Range	1.0-2.0	3.0-5.0	5.9-14.0	163.680	0.001*(S)
Mean	1.41	3.77	9.85		
S.D.	0.26	0.52	2.33		
Hepcidin					
Range	50.0-95.0	95.0-130.0	175.0-320.0	226.221	0.001*(S)
Mean	76.40	105.25	222.89		
S.D.	16.14	51.72	82.69		

S.= serum - NS= Non significant (P-value> 0.05)- S= significant (≤0.05%)

Table (5): Comparison between the three studied groups regarding PV diameter, Caudate span, Spleen span, and fibroscan (number).

Abdominal ultra sound	Control (N=15)	HBV patients (N=20)	HCV patients (N=20)	Test	P
PV. diameter					
Range	10.5-13.0	9.0-15.0	14.0-19.0	53.925	0.001*(S)
Mean	11.79	11.40	15.85		
S.D.	0.24	0.34	0.38		
Caudate.span Range	14.0-14.9	15.0-19.5	9.8-18.4	27.072	0.001*(S)
Mean	14.41	16.25	12.11		
S.D.	0.08	0.37	0.55		
spleen.span Range	9.0-12.4	9.0-14.0	0.5-6.8	274.819	0.001*(S)
Mean	10.73	11.19	1.94		
S.D.	0.24	0.32	0.36		
(Fibroscan)Number					
Range	-	3.5-13.6	3.5-58.0	2.697	0.109(NS)
Mean	-	6.15	11.10		
S.D.	-	0.65	3.02		

NS= Non significant (P-value> 0.05)- S= significant (≤0.05%) – PV= portal vein

4. Discussion

The aim of this study was to evaluate serum iron markers and serum hepcidin levels in patients with chronic hepatitis (B & C) viruses.

The study was conducted on 40 patients with chronic hepatitis (B & C) viruses in addition to 15 as a control group from Menoufia University and National Liver Institute.

There was no significant difference between the three studied groups regarding demographic data which include, age, BMI and sex, the three groups was matched regarding demographic data.

In this study, both AST and ALT show a significant increase in both HBV and HCV patients than the control group, INR show insignificant difference between the three studied groups.

Regarding iron markers, serum iron in the three studied groups show insignificant difference, while serum ferritin show a significant increase in HBV group than the control and HCV, serum transferrin show a significant increase in HCV group more than the other two groups, on the other hand, it was found that there was a significant increase in HBV more than the control group. hepcidin show a significant increase in both HBV and HCV group than the control, also there was a significant increase in HCV group more than the HBV. Which is in agreement with the results of (**16**) and (**17**)? However, other authors did not observe alterations in serum iron levels **(18)**, or they reported a reduction, in liver cirrhosis and hepatocellular carcinoma patients **(19)**. These discrepancies may be because of the differences in stages of liver diseases among the patients in the various studies.

This goes in agreement with **(20)** who stated that serum prohepcidin levels were significantly elevated in CHC patients. **(21)** Reported significant positive correlation between prohepcidin and hepcidin serum levels. There is also evidence that prohepcidin levels are reliable indicators of hepcidin levels and activity **(22).**

(23) Also stated that hepcidin was up-regulated in the liver in response to elevated iron stores and served as a signal to down-regulate iron absorption and increase iron storage.

Also **(24)** noticed a highly significant correlation between hepcidin transcript levels and LIC (Liver Iron Concentration) in the HCV patients.

(25) Mentioned that hepcidin transcription appeared to be regulated by a CCAAT/enhancer-binding protein (C/EBP) element in the 5' flanking region of the mouse and human hepcidin genes. Interestingly, iron loading increases C/EBP-alpha, which may in turn lead to induction of hepcidin.

However our results were not in agreement with **(14)** who stated that Serum hepcidin was significantly lower in CHC patients than in controls. Also **(26)** who found that hepcidin levels did not differ significantly from those in healthy controls, likely because of both methodological imprecision and the very low number of controls enrolled (n=10).

(14) Speculated that hepcidin expression in CHC is determined by the opposing effects of hepcidin-suppressive viral factors and the hepcidin stimulation by iron load. Theoretically, in the early phase of CHC, hepcidin may be prominently suppressed by HCV, but as iron accumulates the negative influence of viral factors may be masked by the positive stimulation of iron.

In our study, there was a positive significant relation between BMI and serum ferritin, serum transferrin and hepcidin. Also there was a positive significant correlation between age and serum transferrin and hepcidin. There was a positive significant correlation between serum transferrin and hepcidin. There was a positive significant correlation between P.V diameter and serum transferrin and hepacidin. There was a positive significant correlation between caudate span and serum ferritin while there was a negative significant correlation with serum transferrin and hepcidin. Spleen span show a positive significant correlation with serum ferritin, and negative significant correlation with serum transferrin and hepcidin. Fib4 show a positive significant correlation with hepcidin. PCR show a negative significant correlation with serum ferritin and positive significant correlation with hepcidin.

Several studies have shown that removing excess iron through therapeutic phlebotomy reduces the severity of hepatic inflammation associated with chronic HCV infection **(27)**. In addition, **(15)** reported that desferrioxamine infusion to achieve a normal serum ferritin level increased the likelihood of a favorable response to treatment in patients with chronic hepatitis B. Accordingly, routine monitoring of serum iron and other iron-associated parameters during clinical management of chronic HBV infection will be helpful in understanding alterations in iron metabolism in HBV and their influence on further liver injury. Elucidation of the association between abnormal serum iron and liver injury may suggest an additional therapeutic approach, such as iron-removal therapy, that could improve the overall efficacy and outcomes of current management of chronic HBV infection with liver injury.

Several studies **(28)** reported that patients with CHC present mild to moderate hepatic iron accumulation, which significantly worsens clinical outcomes, leading to an increased risk of hepatocellular carcinoma. These results are in accordance with several other reports (**16):** suggesting that serum iron markers can represent surrogate

markers for the severity of liver disease; still, these observations should be carefully interpreted, and the level of serum iron markers should be monitored in dynamics, as other interferences cannot be excluded. The interaction between hepcidin (the main regulator of iron homeostasis via the interleukin-6 (IL-6)/STAT3 pathway) and ferroportin (the trans membrane iron transporter) plays crucial roles through down-regulation of iron release from enterocytes and phagocytes; furthermore, mutations in several iron-metabolism related genes may also lead to iron alterations **(29)**.

Regarding hepcidin **(26)** measured hepcidin using a first-generation surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS) assay that was only semiquantitative, with data expressed in arbitrary units. Of note, in that study, hepcidin levels did not differ significantly from those in healthy controls, likely because of both methodological imprecision and the very low number of controls enrolled (n = 15). As a consequence, hepcidin down regulation could be indirectly documented only after normalization for ferritin values, by means of the so-called hepcidin: ferritin ratio **(4)**.

Although our study could not provide insights into the molecular mechanism (s) of hepcidindysregulation in CHC, the results are in agreement with recent elegant studies in animal and cellular models that suggest a direct effect of HCV on liver hepcidin expression.

(30) Studied transgenic mice expressing HVC polyprotein, which showed mild progressive hepatic iron accumulation. These mice had reduced hepcidin messenger RNA (mRNA) expression, which was attributed to HCV protein-induced ROS, with consequent upregulation of an inhibitor of the binding of the transcription factor CCAAT/enhancer-binding protein α (C/EBP-α) to the hepcidin promoter. Similar results were reported in hepatoma cells, where HCV-induced ROS were found to inhibit C/EBP-α through increased histone deacetylase activity **(31)** A possible pitfall of these experimental models was that they could not take into account the effect of inflammation **(32)**, which in CHC patients may counteract ROS-induced hepcidin suppression through the known hepcidinupregulation by proinflammatory cytokines, particularly IL-6 **(33) & (34)**.

Nevertheless, when we analyzed data stratified for iron, we found a significant negative correlation between HCV and serum hepcidin in CHC patients with the lowest iron burden, which gradually disappeared with increasing iron load. We speculate that hepcidin expression in CHC is determined by the opposing effects of hepcidin-suppressive viral factors and the hepcidin stimulation by iron load.

Theoretically, in the early phase of CHC, hepcidin may be prominently suppressed by HCV, but as iron accumulates, the negative influence of viral factors may be masked by the positive stimulation of iron. Because we had no reliable data on disease duration (difficult to obtain in clinical practice) on entry into this cross-sectional study, this hypothesis will require further exploration in studies with appropriate prospective design. However, very recent data suggesting liver iron and s-ferritin as surrogate markers of fibrosis **(35)** and, possibly, of disease duration (**36)** may indirectly support this view.

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