The Egyptian Journal of Hospital Medicine (January 2018) Vol. 70 (9), Page 1518-1528

Role of S-Iron and Ferritin to Predict the Response to Recent New Antiviral Treatment in Chronic Hepatitis C Patients

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ABSTRACT
Background: Chronic hepatitis C (CHC) is an important liver disease, which may progress to cirrhosis or hepatocellular carcinoma. The current treatment regimen for CHC includes pegylated interferon-α (PEG-IFN) combined with ribavirin Ferritin is the major iron storage protein and provides an indirect estimate of the body's iron stores. It is also an established marker for liver iron deposition. **Aim of the Work:** The aim of this study is to configurate the distribution of iron and ferritin levels in patients with chronic hepatitis C virus infection and to conduct a comparative study between the pretreatment and the post treatment iron profile after direct acting antiviral therapies in chronic HCV patients. **Patients and Methods:** This Randomized Controlled Clinical study was conducted on 100 subjects aged from 18 to 60 years selected from Gastroenterology and Hepatology department at Ain Shams University Hospital, Cairo, Egypt, from January 2017 to April 2017 and was approved by the ethical committee. **Results:** The current study suggests that a 12 weeks course of Sofosbuvir / Ledipasvir combination drug therapies showed a higher SVR 12 (92 %) and have significant decrease of the elevated serum iron and ferritin and transferrin saturation to the normal level more than sofosbuvir / Daclatasvir which showed a SVR 12 (88%). In both study groups, patients who showed SVR had significant lower values of Iron, Ferritin and transferrin saturation levels than patients who were non-SVR after end of therapy. **Conclusion:** This study may also shed light on how the changes in serum iron and ferritin levels in chronic hepatitis C patients may be related to HCV treatment. **Recommendations:** Sofosbuvir / Ledipasvir 12-weeks course is more recommended than Sofosbuvir / Daclatasvir 12 weeks course in patients with chronic HCV infection. As serum Iron, serum Ferritin and Transferrin saturation showed more significant improvement with SOF/LED combination therapy than SOF/DAC combination therapy, they are a good markers of highly predictive value in treatment of chronic HCV infected patients with DAAs.
Keywords: serum iron, ferritin, antiviral treatment, CHC.

INTRODUCTION
Hepatitis C virus (HCV) infection which affects nearly 2% of the human population is a major cause of liver disease worldwide. Following acute HCV infection chronicity is 80%. Although many individuals carrying the virus remain asymptomatic, chronicity is accompanied by altered liver function and progressive liver disease ending in cirrhosis or hepatocellular carcinoma in up to 20% of infected subjects [(1)].

Mild - to - moderate iron overload is a common finding among patients with chronic HCV infection where up to 30-40% of them may show increased serum transferrin-iron saturation and serum ferritin or increased hepatic iron concentration [(2)]. Elevated iron indices is correlated with progression of liver disease and a decreased response to antiviral therapy [(3,4)]. Excess iron increases the formation of reactive oxygen species (hydroxyl radicals) leading to lipid peroxidation and damage to protein and DNA resulting in cell membrane and genomic damage and hepatic stellate cell activation and proliferation and upregulate synthesis of smooth muscle actine and collagen thus leading to hepatic fibrogenesis [(5)].

Moreover, iron deposition in hepatocytes enhances HCV replication thus facilitating the viral infection in the liver [(6)].

These hydroxyl radicals generate promutagenic substances such as 8-hydroxyl-2`-deoxy-gusuosine (8-0HDG) which have been implicated in spontaneous DNA mutagenesis and carcinogenesis [(7)]. Therefore, there is need to configurate the distribution of iron and ferritin levels in patients with chronic HCV.

AIM OF THE WORK
The aim of this study is to configurate the distribution of iron and ferritin levels in patients with chronic hepatitis C virus infection and to conduct a comparative study between the pretreatment and the post treatment iron profile after direct acting antiviral therapies in chronic HCV patients.

PATIENTS AND METHODS
Study Design
This study was a Randomized Controlled Clinical Trial conducted on 100 subjects aged from 18 to 60 years selected from Gastroenterology and Hepatology department at Ain Shams University Hospital, Cairo, Egypt,

Received: 20/12/2017
Accepted: 30/12/2017
DOI: 10.12816/0044678

from January 2017 to April 2017 and was approved by the ethical committee.

The subjects were allocated randomly and have been invited to participate in the study after taking a complete informed written consent.

The subjects of both sex were divided into:

Group □: includes 50 patients who were positive for HCV antibodies and positive for HCV RNA (Diseased group), they were classified as a diseased group who have been subdivided into:

Group □a	**Group □b**
Includes 25 patients who received treatment for 12 weeks consists of (Sofosbuvir 400 mg orally once daily + Daclatasvir 60 mg orally once daily)	Includes 25 patients who received treatment for 12 weeks consists of (Sofosbuvir 400 mg orally once daily + Ledipasvir 90 mg orally once daily)

Group □□: includes 50 subjects with age and sex matched control who were negative for HCV antibodies (Control group).

Data Collected before the study:

1. Full detailed Medical History.
2. Clinical Examination.
3. Routine Laboratory Investigations: (CBC, AST, ALT, PT, INR, s. Albumin, Bilirubin, s.Creatinine, Glycated Hemoglobin).
4. Anti HCV Antibodies
5. HCV RNA was done on the diseased group
6. Comparative study was done for the diseased group (□a & □b) regarding estimation of Serum Iron and Ferritin and Transferrin before and after complete treatment mentioned above.

Exclusion Criteria

1. Iron deficiency anaemia or iron therapy.
2. Chronic hemolytic anaemia.
3. Haemochromatosis and haemosiderosis.
4. Chronic renal failure.
5. History of multiple blood transfusions.
6. Chronic alcohol consumption.
7. Immunosuppression.
8. HBV or HIV Coinfection.

The study was approved by the Ethics Board of Ain Shams University.

Statistical Analysis of the data

Data Management and Analysis:

The collected was revised, coded, tabulated and introduced to a PC using statistical package for social sciences IBM SPSS 20.0. Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

I. Descriptive Statistics

1. Mean, Standard deviation (+ SD) and range for parametric numerical data, while Median and Interquartile range (IQR) for non parametric data.
2. Frequency and percentage of non-numerical data.

II. Analytical Statistics

1. **One way ANOVA Test**: was used to assess the statistical significance of the difference of a parametric variable between more than two study groups.
2. **Mann Whitney Test (U test):** was used to assess the statistical significance of the difference of a non parametric variable between two study groups.
3. **Wilcoxon Signed rank test**: was used to compare two related samples, matched samples, or repeated measurements on a single sample to assess whether their populations mean ranks differ.
4. **Kruskal Wallis Test**: was used to assess the statistical significance of the difference of a non parametric variable between more than two study groups.
5. **Chi square test**: was used to examine the relationship between two qualitative variables but when the expected count is less than 5 in more than 20% of the cells; Fisher's Exact Test was used.
6. **Paired t- test:** called dependent sample *t*-test, is a statistical procedure used to determine whether the mean difference between two sets of observations is zero.
7. **Independent sample t-test:** is a parametric test, used to compare the means of two independent groups in order to determine whether there is statistical evidence that the associated population means are significantly different.

P (probability) value = Level of significance:

- P>0.05: Non-significant (NS)
- P<0.05: Significant (S)
- P<0.01: Highly significant (HS)

RESULTS

This study was conducted at Gastroenterology and Hepatology department at Ain Shams University, Cairo, Egypt, from January 2017 to April 2017.

Hundred subjects fulfilling the selection criteria were divided into:

Group □ □Diseased group (50 subjects)

Group □□ □Control group (50 subjects)

Socio-demographic data

Table (1): Comparison between the studied groups □a, □b and group □□ (the control group) as regard gender, Marital status and age

Patient characteristics		Group						Chi square	P-value
		Group □a (SOF/DAC)		Group □B (SOF/LED)		Group□□ (control group)			
		No.	%	No.	%	No.	%		
Gender	Male	13	52.0%	11	44.0%	22	44.0%	0.483	0.785
	Female	12	48.0%	14	56.0%	28	56.0%		
Marital status	Single	3	12.0%	3	12.0%	14	28.0%	4.000	0.135
	Married	22	88.0%	22	88.0%	36	72.0%		
Age		Mean	+ SD	Mean	+ SD	Mean	+ SD	ANOVA	P-value
		48.28	8.16	48.04	8.48	44.02	9.82	2.586	0.081

Table (1) shows that there is no statistically significant difference between **Group□ A (SOF/DAC)**, **Group □B (SOF/LED)** and **group □□ (Control healthy subjects)** as regard Gender, Marital status and Age (P>0.05)

Table (2): Comparison between the studied groups: group □a, group □b and group □□ (control) as regard Blood investigations before treatment

Blood investigations	Group						ANOVA	P-value
	Group A (SOF/DAC)		Group B (SOF/LED)		Control group			
	Mean	+ SD	Mean	+ SD	Mean	+ SD		
HB	13.47	1.97	12.9	1.9	13.45	1.74	0.257	0.799
HCT	39.68	5.71	37.82	5.54	39.47	2.41	0.279	0.768
RBCs	5.12	0.74	4.81	0.68	5.11	0.73	1.482	0.145
WBCs	7.64	1.24	6.92	1.9	7.63	1.25	0.234	0.867
Platelet	223.28	47.93	221.64	48.01	222.27	46.66	0.088	0.93
HbA1c	5.81	1.26	5.92	1.02	5.78	1.24	-1.069	0.29
Serum Creatinine	1.02	0.25	0.89	0.17	0.88	0.16	1.226	0.348
SGOT	34.52	9.85	34.04	9.48	34.41	9.81	0.342	0.734
SGPT	28.64	6.16	26.48	5.62	28.61	7.05	0.77	0.445
PT	14.3	0.93	13.86	0.62	14.28	0.92	1.505	0.187
Albumin	4.18	0.43	4.08	0.38	4.16	0.41	0.558	0.58
INR	1.15	0.07	1.11	0.06	1.13	0.06	1.864	0.168
Total Bilirubin	0.79	0.19	0.72	0.16	0.78	0.18	1.864	0.068
Direct Bilirubin	0.2	0.05	0.2	0.04	0.2	0.05	-0.376	0.709
Indirect Bilirubin	0.6	0.16	0.52	0.13	0.58	0.16	1.834	0.073

Table (2) shows that there is no statistically significant difference between Group □A (SOF/DAC), Group □B (SOF/LED) and control group □□ as regard HB, HCT, RBCs, WBCs, Platelet, HbA1c, Serum Creatinine, SGOT, SGPT, PT, Albumin, INR, Total Bilirubin, Direct and Indirect Bilirubin (P>0.05). before treatment.

Table (3): Comparison between the studied groups: (group a, group b) as regard Blood investigations after treatment

Blood investigations	Group				Independent sample t-test	P-value
	Group A (SOF/DAC)		Group B (SOF/LED)			
	Mean	+ SD	Mean	+ SD		
HB	12.43	1.12	13.11	1.35	-0.267	0.564
WBCs	10.21	3.28	9.12	3.23	0.423	0.732
Platelet	208.40	38.12	211.45	42.12	-0.723	0.421
HbA1c	5.23	.34	5.43	.21	-0.235	0.078
Serum Creatinine	0.48	0.11	0.56	.12	-1.431	0.452
SGOT	31.56	6.67	34.21	8.23	-0.741	0.934
SGPT	29.34	9.12	28.11	7.23	0.653	0.541
PT	11.99	1.41	12.23	.87	-1.214	0.089
Albumin	4.11	.24	3.99	.35	0.363	0.573
INR	1.00	.10	1.18	.03	-1.943	0.412
Total Bilirubin	.91	.23	.85	.08	0.687	0.912
Direct Bilirubin	.34	.10	.31	.03	0.213	0.423
Indirect Bilirubin	.57	.13	.54	.05	1.246	0.682

Table (3) shows that there is no statistically significant difference between Group A (SOF/DAC) and Group B (SOF/LED) as regard HB, HCT, RBCs, WBCs, Platelet, HbA1c, Serum Creatinine, SGOT, SGPT, PT, Albumin, INR, Total Bilirubin, Direct and Indirect Bilirubin (P>0.05). after treatment.

Table (4): Comparison between Iron, Ferritin, Transferrin and Transferrin saturation levels before and after administraion of therapy in the group Ia:

Measurement of variables	Group Ia (SOF/DAC)				Paired t-test	P-value
	Before		After			
Iron	Mean	+ SD	Mean	+ SD		
	272.72	58.69	165.00	24.79	0.742	0.001
Ferritin	320.08	59.21	280.40	20.33	0.631	0.004
Transferrin	198.04	13.79	198.00	13.99	0.438	0.061
Transferrin saturation level	56.84	8.30	42.00	6.48	0.714	0.011

Table (4) shows that there is a statistically significant decrease in serum Iron, Ferritin and Transferrin saturation level after administraion of therapy in the group Ia, ($p < 0.05$). with no statistically significant decrease in transferrin level after administration of therapy ($p > 0.05$).

Table (5): Comparison between Iron, Ferritin, Transferrin and Transferrin saturation levels before and after administraion of therapy in the group Ib:

Measurement of variables	Group Ib (SOF/LED)				Paired t-test	P-value
	Before		After			
Iron	Mean	+ SD	Mean	+ SD		
	285.68	70.42	150.00	24.48	0.821	0.001
Ferritin	331.80	58.67	265.32	15.81	0.764	0.001
Transferrin	197.20	14.68	197.00	14.35	0.417	0.062
Transferrin saturation level	60.16	8.02	38.00	5.48	.458	0.023

Table (5) shows that there is a statistically significant decrease in serum Iron, Ferritin and Transferrin saturation level after administraion of therapy in the group Ib, ($p < 0.05$). with no statistically significant decrease in transferrin level after administration of therapy ($p > 0.05$).

Table (6): Comparison between the Group Ia (SOF/DAC), Group Ib (SOF/LED) and group □□ (control group) as regard Iron, Ferritin, Transferrin and Transferrin saturation levels before administraion of therapy

Measurement of variables before	Group				Group □□ (controlgroup)		Anova test	P-value
	Group Ia (SOF/DAC)		Group Ib (SOF/LED)					
Iron	Mean	+ SD	Mean	+ SD	Mean	+ SD		
	272.72	58.69	285.68	70.42	89.3	13.61	0.456	0.050
Ferritin	320.08	59.21	331.80	58.67	178.21	34.45	0.703	0.045
Transferrin	198.04	13.79	197.20	14.68	189.32	11.48	0.208	0.036
Transferrin saturation level	56.84	8.30	60.16	8.02	28.16	5.02	1.438	0.017

Table (6) shows that there is a significantly highly elevated values of iron, ferritin, transferrin, and transferrin saturation between Group Ia (SOF/DAC), Group Ib (SOF/LED) > group□□ (control group) before administration of therapy ($P < 0.05$).

Table (7): Comparison between the Group Ia (SOF/DAC) and Group Ib (SOF/LED) as regard Iron, Ferritin, Transferrin and Transferrin saturation levels before administration of therapy

Measurement of variables before treatment	Group				Independent sample t-test	P-value
	Group Ia (SOF/DAC)		Group Ib (SOF/LED)			
Iron	Mean	+ SD	Mean	+ SD		
	272.72	58.69	285.68	70.42	-0.456	0.650
Ferritin	320.08	59.21	331.80	58.67	-0.703	0.485
Transferrin	198.04	13.79	197.20	14.68	0.208	0.836
Transferrin saturation level	56.84	8.30	60.16	8.02	-1.438	0.157

Table (7) shows that there is no statistically significant difference between Group Ia (SOF/DAC) and Group Ib (SOF/LED) as regard Iron, Ferritin, Transferrin and Transferrin saturation levels before administration of therapy (P>0.05).

Table (8): Comparison between the Group Ia (SOF/DAC) and Group Ib (SOF/LED) as regard Iron, Ferritin, Transferrin and Transferrin saturation levels after administraion of therapy

Measurement of variables after treatment	**Group**				**Independent sample t-test**	**P-value**
	Group Ia (SOF/DAC)		**Group Ib (SOF/LED)**			
Iron	**Mean**	**+SD**	**Mean**	**+SD**		
	165.00	24.79	150.00	24.48	2.153	0.0364
Ferritin	280.40	20.33	265.32	15.81	2.928	0.005
Transferrin	198.00	13.99	197.00	14.35	0.499	0.062
Transferrin saturation level	42.00	6.48	38.00	5.48	2.357	0.0238

Table (8) shows that there is statistically significant decrease in serum iron, ferritin and transferrin saturation levels in group b > group a after administration of therapy (P< 0.05). with no statistically significant decrease in transferrin level between group a and group b after administration of therapy (p > 0.05).

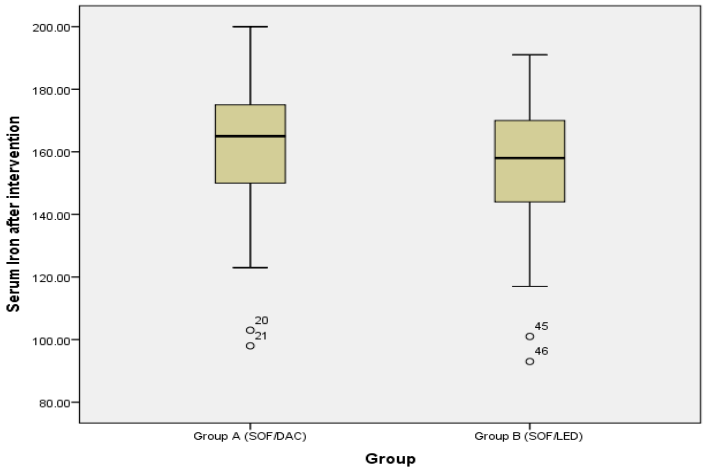

Figure (1): Comparison between Group Ia (SOF/DAC) and Group Ib (SOF/LED) as regard Serum iron level after administration of therapy

Figure (1) shows that there is a statistically significant decrease **in Serum iron level after administration of therapy in group b > a** (P<0.05)

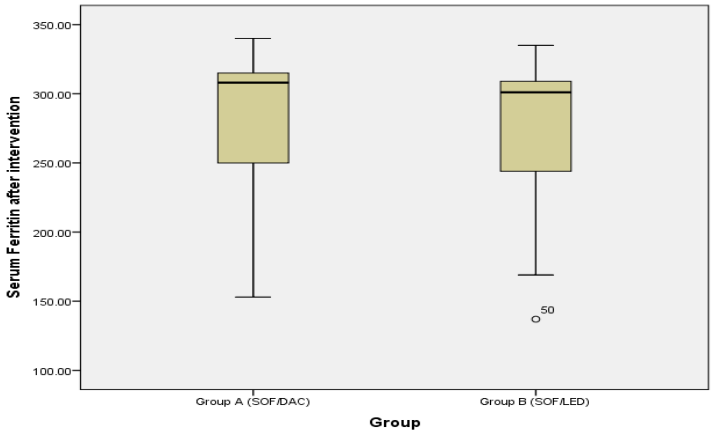

Figure (2): Comparison between Group Ia (SOF/DAC) and Group Ib (SOF/LED) as regard Serum Ferritin levels after administration of therapy

Figure (2) shows that there is a statistically significant decrease **in Serum ferritin level after administration of therapy in group b > a** (P<0.05)

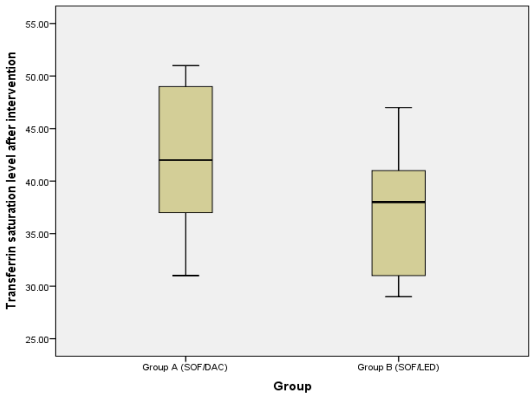

Figure (3): Comparison between group A (SOF/DAC) and group B (SOF/LED) as regard Transferrin saturaion levels After administraion of therapy

Figure (3) shows that there is a statistically significant decrease in **Transferrin saturaion levels** after **administraion of therapy** in group b > group a (P<0.05).

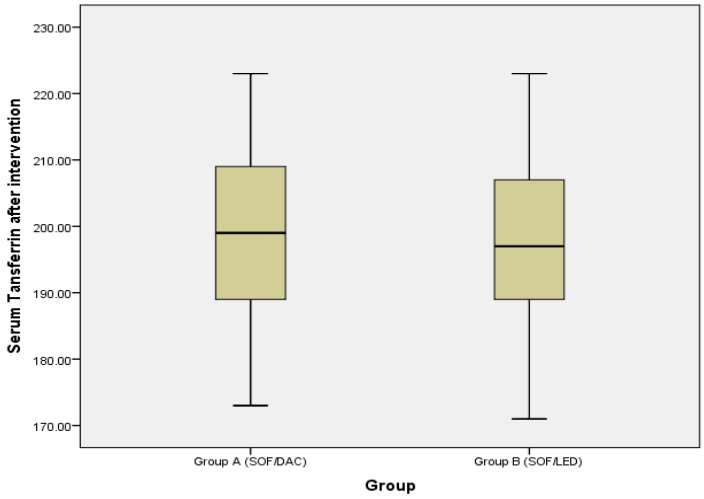

Figure (4): Comparison between Group Ia (SOF/DAC) and Group Ib (SOF/LED) as regard Serum Transferrin levels after administration of therapy

Figure (4) shows that there is no statistically significant decrease in Serum Transferrin level after administration of therapy (P>0.05) in group a and group b.

Table (9): Comparison between the studied groups (group □a and group □b) as regard HCV PCR

Blood investigations	Group □				Independent sample t-test	P-value
	Group □A (SOF/DAC)		Group □B (SOF/LED)			
	Mean	+ SD	Mean	+ SD		
HCV PCR quantitative before ×10³	678.12	11.34	889.23	14.25	0.367	0.867
HCV PCR quantitative after ×10³	2.11	1.34	1.900	1.21	0.214	0.064
p-value	0.001		0.001			

Table (9) shows that there is no statistically significant difference between Group □A (SOF/DAC) and Group □B (SOF/LED) as regard HCV PCR before start of therapy as well as after completion of treatment (P>0.05). Additionally both groups had no statistically significant difference after treatment in each group; however each group showed highly significant decline in the mean quantitative value of HCV PCR after end of therapy.

Table (10): Correlation between Iron, Ferritin, Transferrin and Transferrin saturation levels and HCV PCR after end of therapy in group 1a:

Measurement of variables	Group Ia				Paired t-test	P-value
	SVR N=22 (88%)		No-SVR N=3 (12%)			
Iron	Mean	+ SD	Mean	+ SD		
	91.16	12.11	152.00	25.21	0.631	0.0001
Ferritin	231.36	26.23	356.12	34.23	0. 458	0.001
Transferrin	198.04	13.79	197.21	13.21	0.438	0.061
Transferrin saturation level	28.03	2.01	61.02	5.15	0.728	0.011

Table (10) shows that in the group Ia, the patients who showed SVR had significant lower values of Iron, Ferritin and Transferrin saturation levels than patients who were non-SVR after end of therapy. (p< 0.05). with no decrease in transferrin level (p > 0.05).

Table (11): Correlation between Iron, Ferritin, Transferrin and Transferrin saturation levels and HCV PCR after end of therapy in group 1b:

Measurement of variables	Group Ib				Paired t-test	P-value
	SVR, N=23 (92%)		No-SVR, N=2 (8%)			
Iron	Mean	+ SD	Mean	+ SD		
	94.12	23.12	156.00	24.21	0.751	0.0001
Ferritin	245.21	37.12	334.23	45.21	0. 7865	0.003
Transferrin	197.00	14.35	199.00	13.14	0.417	0.062
Transferrin saturation level	33.01	7.01	65.02	1.16	0.328	0.021

Table (11) shows that in the group **Ib**, the patients who showed SVR had significant lower values of Iron, Ferritin and Transferrin saturation levels than patients who were non-SVR after end of therapy, (p < 0.05). with no decrease in transferrin level (p > 0.05)

DISCUSSION

The current work was prepared to compare between serum iron together with serum ferritin and transferrin saturation levels in 100 subjects, of both sex, who have been divided into two; the diseased group concluded 50 patients who were positive for HCV antibodies and positive for HCV RNA and the control group which contained 50 subjects with matched age and sex who were negative for HCV antibodies. Furthermore, the diseased group was subdivided into 2 other groups as regard specific treatment agents (25 patients who received Sofosbuvir 400 mg orally once daily plus Daclatasvir 60 mg orally once daily for 12 weeks (group IA) versus 25 patients who received Sofosbuvir 400 mg orally once daily + Ledipasvir 90 mg orally once daily for 12 weeks (group IB).
Up to the knowledge till now there was no study had been carried out to compare serum iron and ferritin in Sofosbuvir / Daclatasvir versus Sofosbuvir / Ledipasvir combination drug therapies group patients.

In the current study there was no statistically significant difference regarding Age between both groups, (table 8), (P > 0.05), this is in agreement with **Abdel Latif *et al.*** [8] and **Elshazly *et al.*** [9], there was no statistically significant difference regarding Gender between both groups, (table 8), (P > 0.05), this is in agreement with **Abdel Latif *et al.*** [8]; and there was no statistically significant difference regarding Marital state between both groups, (table 8), (P > 0.05).

Before treatment the mean value of iron was noted to be elevated and matched in both study groups, no statistically significant difference was existed between diseased groups, (table 14), but was not elevated in the control subjects group □□, (table 13). The results were in agreement with Bazeed et al. [10] who reported that before start therapy, no statistically significant difference was existed between group who received sofosbuvir, interferon and ribavirin. After treatment there was significant decrease regarding the values of serum iron in both groups to normal values, with more decrease of serum iron in group 1b than group 1a (table 15, figure 1). This is in contrast to Bazeed et al. [10] who revealed in his study that, in case of patients treated with Sofosbuvir, ribavirin and pegylated interferon for 12 weeks, a significant increase in serum iron level after treatment but it did not reach the upper limit of normal.

These results were explained in the same study by the shorter duration of interferon therapy compared to the old regimen of 48 weeks, so little hepcidin (the iron regulatory hormone) production resulting in little reduction in serum iron. Also, this increase in serum iron may be due to ribavirin induced hemolytic anemia that increases serum iron because red blood cells are being destroyed too quickly [11]; This is in agreement with **Bernutha *et al.*** [12] who noticed Serum iron, despite being also decreased, no significant difference was revealed ($p = 0.117$)

Before treatment the mean value of serum ferritin was noted to be elevated and matched in both study groups, no statistically significant difference was existed between group 1a and 1b, (p> 0.05), (table 14), but was not elevated in the control healthy subjects group □□, (table 13). The results were in agreement with **Bazeed *et al.*** [10] who reported that before start therapy, no statistically significant difference was existed between groups who received sofosbuvir, interferon and ribavirin. After treatment there was significant decrease regarding the values of serum ferritin in both groups to normal values, (p< 0.05), (table 15, figure 2), with more decrease of serum ferritin in group 1b than group 1a,. The results were in agreement with **Bazeed *et al.*** [10] who reported that the group received sofosbuvir showed an extremely significant lower value of serum ferritin than the normal control group.

Also, the study is in agreement with Bernutha et al [12] who has noted a reduction in serum ferritin levels from baseline to end of therapy ($p < 0.001$)

Before treatment the mean value of Transferrin level and saturation were noted to be elevated and matched in both study groups, no statistically significant difference was existed between group 1a and 1b, (p > 0.05), (table 14), but was not elevated in the control healthy subjects group □□, (table 13), this is in agreement with Bernutha et al [12], who noticed no statistically significat difference as regard serum transferrin level and saturation in groups before treatment. After treatment there was significant decrease regarding the values of serum transferrin saturation level in both groups to normal values, with more decrease in group 1b than group 1a, (p< 0.05), (table 15, figure 3), but with no statistically significant difference between group 1a and group 1b as regard serum transferrin level after therapy, (p> 0.05), (table 15, figure 4), this is in contrast to Bernutha et al [12], who noticed transferrin saturation showed normal values at both time points (baseline = 28.9% and SVR12 = 27.3%, respectively) and therefore decreased by 5.5% ($p = 0.071$). Transferrin increased from 2.81 to 2.97 g/l ($p = 0.583$).

Bitar and Dbaibo [2] reported that mild-to-moderate iron overload is a common finding among patients with chronic HCV infection; indeed, up to 30–40% of them may show increased serum transferrin-iron saturation and serum ferritin or increased hepatic iron concentration. On the other hand, elevated iron indices have been correlated with a progression of the liver disease and a decreased response to antiviral therapy [13].

In current study it was denoted that LED/SOF combination has favorable adverse effect profile not leading to drug discontinuation like fatigue, headache, nausea, diarrhea, and insomnia, which is in agreement with European Association for the Study of Liver 2015 [14].

The group Ia, SVR 12 was 88 % *Versus* SVR 12 was 92 % in group 1b, the patients who showed SVR in both groups, had significant lower values of Iron, Ferritin and Transferrin level, Transferrin saturation levels than patients who were non-SVR after end of therapy, (table 17, 18). SVR 12 (defined as undetectable HCV-RNA, 12 weeks after the completion of therapy by a sensitive HCV-RNA assay [15]. This current study is in agreement with **Abd El Latif *et al.*** [8], who noticed that SVR 12 was achieved by 90 % in group received sofosbuvir / simeprevir regimen and 77 % in group received sofosbuvir / ribavirin regimen. Also, in agreement with **Willemse *et al.*** [16], who noticed that SVR 12 was 92 % in group received sofosbuvir / simeprevir regimen for 12 weeks. There was no statistically significant difference between both groups regarding the baseline and after treatment Hb level, ($p > 0.05$), (table 9, 10). This is in agreement with **Abd El Latif *et al.*** [8], who noticed that Hb doesn't fall down in group taking sofosbuvir / semiprevir versus group received sofosbuvir / ribavirin who showed significant decrease in Hb due to ribavirin hemolytic anemia which is one of the most significant adverse reaction of ribavirin.

There was no statistically significant difference in platelets count before and after treatment in both studied groups, ($p > 0.05$), (table 9, 10), this is in agreement with **Gane *et al.*** [17] and **Abd El Latif *et al.*** [8], who noticed no change in platelets count throughout his study on sofosbuvir / ribavirin regimen. But in contrast to **Ruane *et al.*** [18], who noticed that the platelets count increased during treatment with sofosbuvir / ribavirin regimen and in contrast to Apurva et al. [19] who noticed decreased platelets count with sofosbuvir / simeprevir regimen.

There was no statistically significant difference in Total leucocytic count before and after treatment in both studied groups, ($p > 0.05$), (table 9, 10), and this is in agreement with **Gane *et al.*** [17], **Abd El Latif *et al.*** [8] who noticed no change in Total Leucocytic count throughout his study on sofosbuvir / ribavirin regimen.

There was no statistically significant difference in INR before and after treatment in both studied groups ($p > 0.05$), (table 9, 10), this is in agreement with **Apurva *et al.*** [19], **Abd El Latif *et al.*** [8] who noticed no change in INR with sofosbuvir / simeprevir regimen.

There was no statistically significant difference in Bilirubin before and after treatment in both studied groups, ($p > 0.05$), (table 9, 10), this is in agreement with **Abd El Latif *et al.*** [8], who noticed no statistically significant difference between both groups (sofosbuvir / simeprevir group & sofosbuvir / ribavirin) and in contrast to **Apurva *et al.*** [19] who noticed increased bilirubin with sofosbuvir / semiprevir regimen.

There was no statistically significant difference regarding ALT and AST before and after treatment in both studied groups, ($p > 0.05$), (table 9, 10), this is in agreement with ***Perumalswami et al.*****and Abd El Latif *et al.*** [8] who noticed no statistically significant difference between study groups regarding the baseline and end-of- treatment levels of ALT and AST, who discovered also elevation in ALT and AST during treatment with sofosbuvir / simeprevir regimen which is higher than ontreatment with sofosbuvir / ribavirin regimen.

CONCLUSION

Results of the current study suggest that a 12 weeks course of Sofosbuvir / Ledipasvir combination drug therapies showed a higher SVR 12 (92 %) and have significant decrease of the elevated serum iron and ferritin and transferrin saturation to the normal level more than sofosbuvir / Daclatasvir which showed a SVR 12 (88 %). In both study groups, patients who showed SVR had significant lower values of Iron, Ferritin and Transferrin saturation levels than patients who were non-SVR after end of therapy.

This study may also shed light on how the changes in serum iron and ferritin levels in chronic hepatitis C patients may be related to HCV treatment.

RECOMMENDATIONS

Sofosbuvir/Ledipasvir 12-weeks course is more recommended than Sofosbuvir / Daclatasvir 12 weeks course in patients with chronic HCV infection. As serum Iron, serum Ferritin and Transferrin saturation showed more significant improvement with SOF/LED combination therapy than SOF/DAC combination therapy, they are a

good markers of highly predictive value in treatment of chronic HCV infected patients with DAAs. Further prospective randomized trials should be performed to find the role of serum iron and ferritin to predict the response of treatment with 12 –weeks course of Sofosbuvir / Ledipasvir or 12-weeks course of Sofosbuvir / Daclatasvir combination drug therapies.

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