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Diabetes Mellitus as a Risk Factor in Patients with Chronic Liver Diseases-Biochemical Studies: Part 1

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ABSTRACT

Biochemical parameters such as blood sugar, alanine aminotransferase, albumin, bilirubin, anti-oxidant enzymes, aspartate aminotransferase, serum super oxide mutes (SOD), catalase (CAT) concentration, glutathion (GSH), malondialdhyde (MDA) cortisol hormone and interleukin-6 for three groups of Egyptian voluntary patients aged 18-60 years (mixture of males and females) have been monitored and investigated. The experiment included three groups as such: Group 1: Healthy control: served as healthy subjects and they did not show any clinical or biochemical disorders. Group 2: patients control with liver cirrhosis, and group 3: as patient with liver cirrhosis associated with diabetes mellitus (DM). The results showed that DM accelerates liver fibrosis and inflammation and giving rise to more severe liver failure and may potentiate the incidence of bacterial infections in cirrhotic patients which may associated with increased mortality.

Keywords: Liver cirrhosis; Diabetes mellitus; Chronic infections with hepatitis C virus

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INTRODUCTION

Cirrhosis is a condition in which the liver does not function properly due to long-term damage. This damage is characterized by the replacement of normal liver tissue by scar tissue. Typically, the disease develops slowly over months or years. Early on, there are often no symptoms as the disease worsens, a person may become tired, weak, itchy, have swelling in the lower legs, develop yellow skin, bruise easily, have fluid build-up in the abdomen, or develop spider-like blood vessels on the skin. The fluid build-up in the abdomen may become spontaneously infected. Other complications include hepatic encephalopathy, bleeding from dilated veins in the esophagus or dilated stomach veins, and liver cancer. Hepatic encephalopathy results in confusion and may lead to unconsciousness according to Lancet 2015. Cirrhosis is most commonly caused by alcohol, hepatitis B, hepatitis C, and non-alcoholic fatty liver disease, which has a number of causes, including being overweight, diabetes, high blood fats, and high blood pressure. A number of less common causes of cirrhosis include autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, certain medications, and gallstones. Diagnosis is based on blood testing, medical imaging, and liver biopsy according to Lancet 2016. Chronic infections with the hepatitis C virus represent a major global health problem, with around 170 million patients at risk of developing life-threatening complications such as liver cirrhosis or hepatocellular carcinoma [1]. In Lancet 2015 Cirrhosis affected about 2.8 million people and resulted in 1.3 million deaths Of these, alcohol caused 348,000, hepatitis C caused 326,000, and hepatitis B caused 371,000. Moreover, HCV infection and its complications are among the leading public health challenges in Egypt [2]. A recent study by Mahmoud et al. concluded that Egypt is confronted with an HCV disease burden of historical proportions that distinguishes this nation from others. Egypt has possibly the highest HCV prevalence in

the world; 10%-20% of the general population is infected and HCV is the leading cause of HCC and chronic liver disease in the country. Approximately 90% of Egyptian HCV isolates belong to a single subtype, 4a, which responds less successfully to interferon therapy than other subtypes [3]. Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period [4]. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications [5]. Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes [6]. As of 2015, an estimated 415 million people had diabetes worldwide [7]. HCV infection has high comorbidity with diabetes mellitus (DM), a metabolic disorder characterized by deregulation of blood sugar and insulin. In addition, epidemiological studies suggested that DM confers a 2- to 3-fold increase in HCC risk in patients with CHC, regardless of whether the patient has undergone curative hepatectomy or antiviral therapy [8]. (DM) worsens the clinical course of liver cirrhosis. That DM accelerates liver fibrosis and inflammation giving rise to more severe liver failure and may potentiate the incidence of bacterial infections in cirrhotic patients which are associated with increased mortality [9].

EXPERIMENTAL SECTION

This was a prospective, single-armed, self-controlled pilot study, conducted at Tropical medicine and Gastroenterology Department, Minia University Hospital, El minia, Egypt.

Patients

Forty volunteer patients with proven liver cirrhosis, liver cirrhosis with diabetes mellitus (DM), who were selected from admitted patients at Tropical medicine and gastroenterology, Minia University Hospital were eligible for the study. Furthermore, twenty clinically healthy subjects were included in the study as a healthy control group.

Patients grouping: The included patients and controls were classified into three groups each comprising twenty patients as follows; Group 1- (Healthy control): served as healthy subjects and they did not show any clinical or biochemical disorders. Group 2- (patients control with liver cirrhosis). Group 3- (patient with liver cirrhosis and diabetes mellitus).

Sample Collection

Venous blood sample was collected from each subject using a sterile plastic syringe. The blood put in tube and allowed being clot then centrifuged to separate the serum, for the other tests. All biochemical parameters were done in Minia university hospital lap, except anti-oxidant enzymes, cortisol hormone and interleukin-6 were carried out in Elkasr Eleni hospital lap. Full history taking with special emphasis on suggestive symptoms of liver cell failure (jaundice, ascites, lower limb edema), suggestive symptoms of portal hypertension (e.g. previous history of bleeding varies). Clinical examination with stress on the clinical signs of liver cirrhosis (firm sharp bordered liver), signs of liver cell failure (e.g. palmer erythema and flapping tremors), and signs of portal hypertension (e.g. ascites, splenomegaly, and lower limbs edema). Inclusion criteria: Males and females ages (18-60 years). Liver cirrhosis patients and Liver cirrhosis with diabetes mellitus patient.

Exclusion criteria: patient with hepatic encephalopathy. patient with renal failure. Patients with serious complications in the heart, kidneys, or lungs. Patients with autoimmune diseases, such as autoimmune hepatitis. All data are expressed as Mean ± SE. Numbers of samples in each group are twenty. Values in the same raw which share the same superscript symbol are not significantly different.

RESULTS AND DISCUSSION

This study reveals number of important findings reflecting the influence of diabetic mellitus (DM) on liver cirrhosis (LC) and its impact on the biochemical factors. The results showed a significant increase in the random blood sugar in LC with DM group compared with that in control or non-diabetic groups (Figure 1and Table 1). These results are in agreement with other studies which proved that altered insulin signaling chronic hyperglycemia may cause oxidative stress and cellular damage [10-12]. It was also reported that, as the liver plays a crucial role in glucose metabolism, and responsible for the balance of blood glucose levels by means of glycogenogenesis and glycogenolysis [13], so it is not surprising that DM is an epiphenomenon of many chronic liver diseases such as chronic hepatitis, fatty liver, liver failure and cirrhosis [14].

Table 1: Random blood sugar, interleukin-6 and cortisol among different groups

Groups	Random Blood sugar (mg/dL)	Interleukin-6 (pg/ml)	Cortisol (ug/dL)
Control	112.5 ± 4.78a	34.49 ± 1.67a	9.16 ± 0.56a
Liver cirrhosis(LC)	118 ± 6.14a	131.09 ± 7.8b	23.07 ± 2.69b
Liver cirrhosis/Diabetes mellitus (LC/DM)	363.3 ± 29.5c	166.73 ± 9.86c	19.24 ± 1.88b
LSD	19.92	12.44	2.71

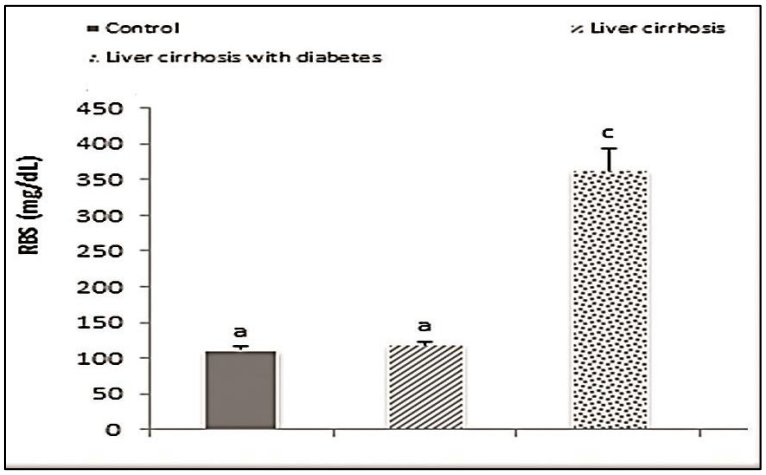

Figure 1: Random blood sugar concentration among different groups

The random blood sugar in control group is (112.5 ± 4.78), in liver cirrhosis group is (118 ± 6.14) and in liver cirrhosis with diabetes mellitus group (363.3 ± 29.5). The significant increase in random blood sugar in LC with D.M. group (363.3 ± 29.5) than LC group (118 ± 6.14) indicating that the metabolic homeostasis of glucose is impaired as a result of some disorders such as insulin resistance, glucose intolerance and diabetes [15]. It means, development of chronic liver disease may lead to glucose intolerance and occasionally diabetes [16]. This confirmed that 96% of patients with cirrhosis are glucose intolerant and 30% may be clinically diabetic. This also, concluded that, cirrhosis itself is associated with glucose intolerance and diabetes or on other hand; HCV is associated with an increased risk of diabetes [17].

Many studies indicated a big role for IL-6 in the process of liver damage and carcinogenesis. IL-6 levels were frequently elevated in patients with LC. Also, serum IL-6 levels are elevated in patients with chronic liver inflammation including alcoholic hepatitis, HBV, HCV infections, and steatohepatitis. The present study showed that serum levels of IL-6 were significantly higher in all patients groups compared with control group (Figure 2). Thus, circulating IL-6 titers in liver cirrhosis with diabetes group recorded 166.73 ± 9.86 compared with cirrhotic (131.09 ± 7.89) and control groups (34.49 ± 1.67) (Table 1 and Figure 2). These results are in agreement with other studies which confirmed that the duration of DM with LC acts as a direct risk factor in increasing IL-6 level [11,18-21].

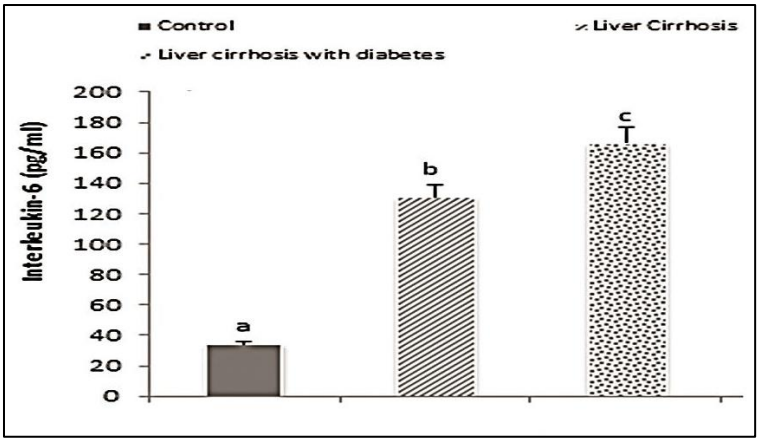

Figure 2: Interleukin-6 concentration among different groups

The Interleukin-6 in patients with liver cirrhosis and diabetes mellitus group (166.73 ± 9.86); liver cirrhosis group (131.09 ± 7.89) and the normal control group (34.49 ± 1.67). Adrenal insufficiency (AI) is defined as deficient production or action of glucocorticoids resulting from either a structural damage of adrenal glands, ''primary adrenal failure'' or an impairment of the hypothalamic-pituitary axis or ''secondary adrenal disease [22]. In patients with cirrhosis, adrenal insufficiency (AI) is reported during sepsis and septic shock and is associated with increased mortality. Consequently, the term ''hepato-adrenal syndrome'' was proposed. Some studies have shown that AI is frequent in stable cirrhosis as well as in cirrhosis associated with decompensation other than sepsis, such as bleeding and ascites [23]. In critically ill patients, there is a relatively adrenal insufficiency (RAI), which is an inadequate glucocorticoid activity depending on the severity of illness. This term has been replaced by critical illness-related corticosteroid insufficiency (CIRCI), which is a reduced adrenal steroid production or tissue resistance to glucocorticoids in patients with systemic inflammation [24]. AI could be a feature of liver disease (i.e., hepato-adrenal syndrome) [25]. However, there is a relationship between cirrhosis and adrenal insufficiency through a reduction in adrenal dysfunction in patients with acute hepatic necrosis [26].

As liver is primary site of adrenal steroid hormone metabolism and cholesterol synthesis, so the cortisol concentration reflects the liver status. This study confirmed that there are a significant increase in cortisol titers in liver cirrhosis group (23.07 ± 2.69) and liver cirrhosis with diabetes mellitus (DM) group (19.24 ± 1.88) compared with control group (9.16 ± 0.56) (Table 1 and Figure 3). This increase in cortisol is attributed to the frequent dysfunction of hypothalamus-pituitary-adrenal (HPA) in patients with liver disease in both of acute critical illness (e.g., sepsis, shock, and variceal bleeding) and stable cirrhosis [27]. This concluded that liver disease may lead to progressive impairment of the HPA axis [28,29].

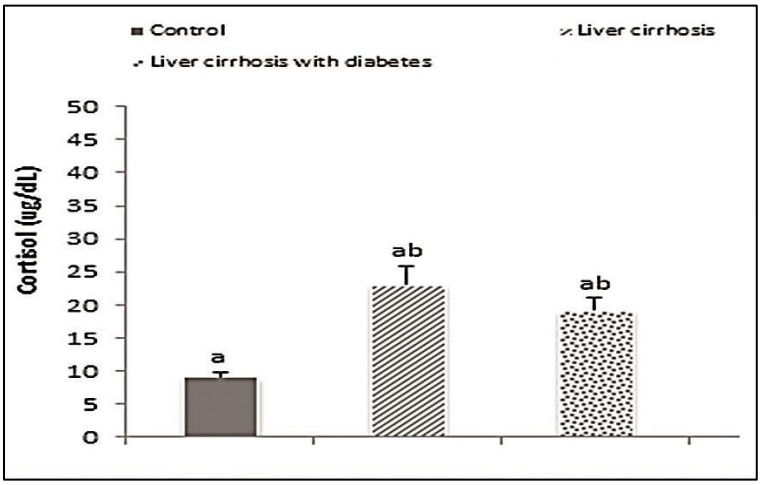

Figure 3: Cortisol concentration among different groups

Cortisol concentration in control group is (9.16 ± 0.56), in patients with liver cirrhosis is (23.07 ± 2.69) and in patients with liver cirrhosis with diabetes mellitus is (19.24 ± 1.88).

Alanine transferase enzyme (ALT) and aspartate transferase enzyme (AST) activities are important biological markers that are widely used for liver diseases. The present investigation showed a significant increase in serum liver enzymes activity ALT, AST (Table 2 and Figures 4 and 5). Thus, a significant increase in serum aspartate aminotransferase (AST) in liver cirrhosis with diabetes mellitus group (95.6 ± 16.91) but was a moderate in liver cirrhosis group (58.98 ± 7) comparable to control group (31.06 ± 2.38). Also, the present investigation showed that there is a significant increase in serum aspartate aminotransferase (AST) in liver cirrhosis with diabetes mellitus group (95.6 ± 16.91) while in cirrhosis group was moderate (58.98 ± 7) compared to control group (31.06 ± 2.38).

Serum alanine aminotransferase (ALT) in control group is (31.06 ± 2.38), liver cirrhosis with diabetes mellitus group is (69 ± 16.23), and for liver cirrhosis group is (58.98 ± 7).

Table 2: Liver function among different groups

Groups	Alanine aminotransferase (U/L)AST	Aspartate aminotransferase (U/L)AST	Albumin (g/dL)	Total. Bilirubin (U/L)	Direct. Bilirubin (U/L)
Control	31.06 ± 2.38a	31.94 ± 1.44a	4.3 ± 0.15d	0.67 ± 0.038a	0.52 ± 0.04a
Liver cirrhosis(LC)	58.98 ± 7ab	68.56 ± 8.31ab	2.48 ± 0.07c	1.78 ± 0.25b	1.01 ± 0.14ab
Liver cirrhosis/Diabetes mellitus (LC/DM)	69 ± 16.23b	95.6 ± 16.91b	2.2 ± 0.025b	2.32 ± 0.34bc	1.36 ± 0.23bc
LSD	17.3	24.86	0.11	0.5	0.37

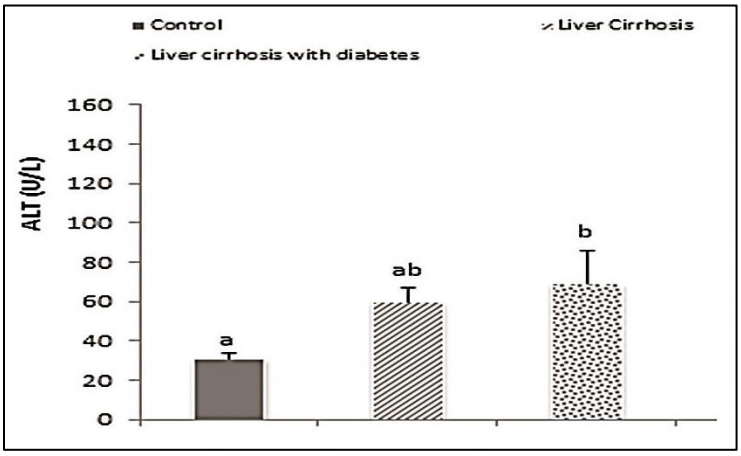

Figure 4: Alanine aminotransferase (ALT) concentration among different groups

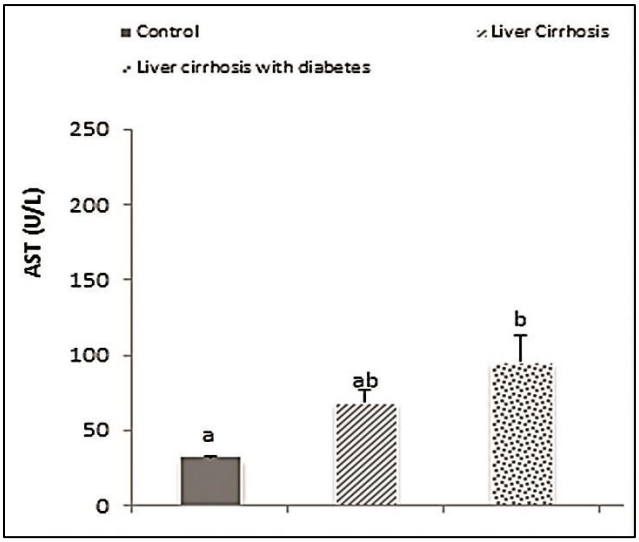

Figure 5: Aspartate aminotransferase (AST) concentration among different groups

In serum, aspartate aminotransferase (AST) in liver cirrhosis with diabetes mellitus group (95.6 ± 16.91); in liver cirrhosis group (58.98 ± 7) and in control group (31.06 ± 2.38).

The results showed also, the serum direct bilirubin (DB) concentration and serum total bilirubin (Figure 6) (TB) concentration (Table 2 and Figure 7) of all groups compared to healthy group are in agreement with the reported study [30] which revealed that damaged liver cells could lead to a significant increase in these enzymes activities. Thus, the serum tdirect bilirubin DB level in liver cirrhosis group was 1.01 ± 0.14 while in liver cirrhosis with diabetes mellitus group was dramatically increased into 1.36 ± 0.23 compared to the control healthy group 0.52 ± 0.04 as seen in Table 2 and Figure 6. Also, the study showed that serum TB is a moderate level in liver cirrhosis group (1.78 ± 0.25) but increased significantly in liver cirrhosis with diabetes mellitus group (2.32 ± 0.34) compared

to the control group (0.67 ± 0.03) (Table 2 and Figure 7). These results are also in agreement with other study [29] explained increase in hepatic cell membrane fluidity could lead to enzyme release into circulation and eventually lead to enzymes activity elevation in serum. The increased levels of serum bilirubin (either DB or TB) indicate impaired excretory and synthetic functions of the liver [31]. Increased serum bilirubin level is a result of liver dysfunction and hyperbilirubinemia [32].

Direct Bilirubin in control group is (0.52 ± 0.04), in liver cirrhosis with diabetes mellitus group (1.36 ± 0.23) and in liver cirrhosis group is (1.01 ± 0.14).

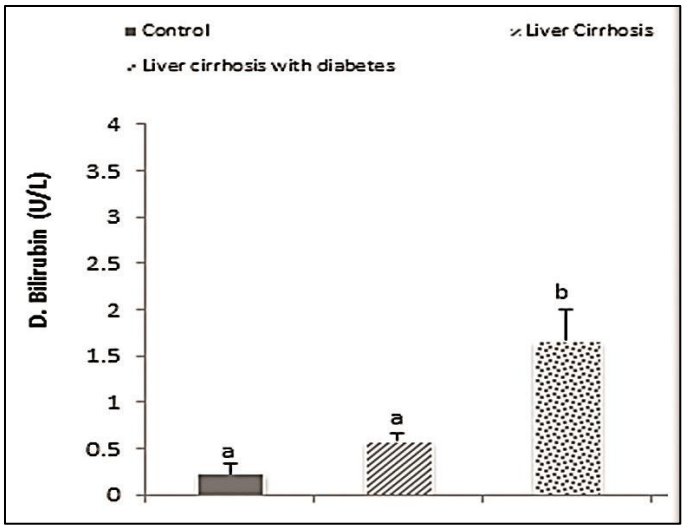

Figure 6: Serum direct bilirubin (DB) among different groups

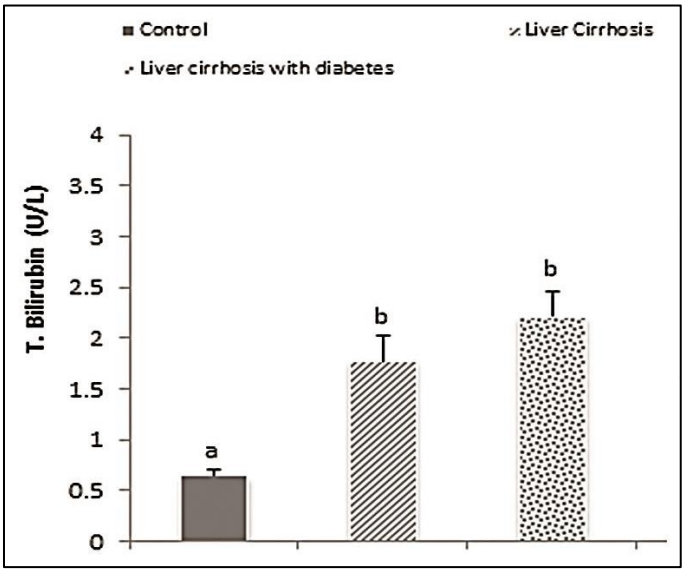

Figure 7: Total bilirubin concentration among different groups

Total Bilirubin in control group (0.67 ± 0.03), in liver cirrhosis with diabetes mellitus group (2.32 ± 0.34) and in liver cirrhosis group (1.78 ± 0.25).

Serum albumin is the most abundant plasma protein and is essential for maintaining oncotic pressure of the vascular system. As albumin is usually produced by hepatocytes which are produced in the liver, so the injury resulted from liver disease decrease the serum albumin level. So, serum albumin can be considered a useful tool in clinical scores, for evaluating liver function [29]. Such fact has been recognized in the present study as well. Thus, the liver cirrhosis group showed a decreased albumin at 1.78 ± 0.25 while for patient with cirrhosis and diabetes mellitus was at 2.32 ± 0.34 compared to the healthy group at 0.67 ± 0.03 (Table 2 and Figure 8).

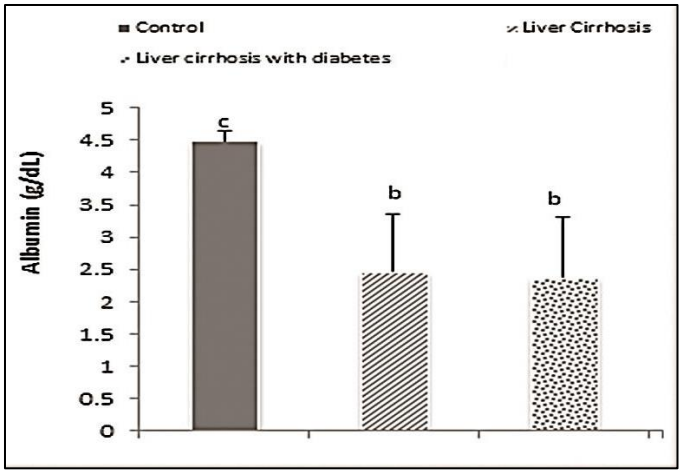

Figure 8: Albumin concentration among different groups

Serum albumin in control group is (4.3 ± 0.15), in liver cirrhosis with diabetes mellitus group (2.2 ± 0.02) and in liver cirrhosis group (2.48 ± 0.07) (Figure 8). In the body, oxidation reactions generally involve highly reactive molecules called free radicals which re-side primarily in the mitochondria of cells. When free radicals are released from the mitochondria in number sufficient to overwhelm the protective biochemical system of the body, they become a threat to some cellular structure such as lipids, proteins, carbohydrates, membrane components, which are particularly vulnerable and also nucleic acids in cells embraces according to World Health Organization. Antioxidant reacts with the free radicals before they are able to react with other molecules that providing protection from oxidant reactions according to Association of Clinical 2002. The free radicals can also start chain reactions in the cell, and this could cause damage or death. Antioxidants which are molecules capable of inhibiting the oxidation of other molecules terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions. They do this by being oxidized themselves, so antioxidants are often reducing agents [33].

Increased production of oxygen free radicals occurs in pathological states such as inflammation or transient ischemia with reperfusion. According to World Health Organization, 2015, the body protects itself against oxygen free radical toxicity by enzymatic mechanisms (superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH)) and by non-enzymatic ones (antioxidant, vitamins, uric acid, albumin, bilirubin, and many others). SOD, a metallo-enzyme, plays a key role in defending cells against oxygen radical toxicity.

In our study there are a significant decrease in Serum SOD, CAT and GSH (Table 3 and Figures 9). Thus serum super oxide mutes (SOD) in control group was 1.96 ± 0.17, and significantly decrease in both of liver cirrhosis group at 0.36 ± 0.04 and liver cirrhosis with diabetes mellitus group at 0.37 ± 0.08 (Table 3 and Figure 9). Similarly, serum Catalase (CAT) in control group was 123.61 ± 2.12, then showed a significant decrease in liver cirrhosis group at 51.81 ± 7.75 and in liver cirrhosis with diabetes mellitus group at 53.39 ± 8.04 (Table 3 and Figure 10). Same effect has been also recognized regarding serum Glutathione (GSH) concentration which recorded 59 ± 1.88 in control group then decreased significantly into 31.29 ± 1.25 in liver cirrhosis group and into 38.45 ± 3.62 in liver cirrhosis with diabetes mellitus group (Table 3 and Figure 11). These results are agreed with the reported studies [34-36] which revealed that oxidative stress is a common pathogenetic mechanism contributing to initiation and progression of hepatic damage in a variety of liver disorders such as alcoholic liver disease, chronic viral hepatitis, autoimmune liver diseases and non-alcoholic steatohepatitis. During the progression of HCV infections, reactive oxygen species are generated, and these then induce significant DNA damage and the development of hepatocellular carcinoma.

Table 3: Some anti-oxidants enzymes among different groups

Groups	SOD	CAT	GSH	MDA
Control	1.96 ± 0.15^{b}	123.61 ± 2.12^{b}	59 ± 1.88^{c}	2.15 ± 0.48^{a}
Liver cirrhosis(LC)	0.36 ± 0.04^{a}	51.81 ± 7.75^{a}	31.29 ± 1.25^{a}	11.52 ± 0.53^{b}
Liver cirrhosis/Diabetes mellitus (LC/DM)	0.37 ± 0.08^{a}	53.39 ± 8.04^{a}	38.45 ± 3.62^{ab}	9.79 ± 1.08^{b}
LSD	0.14	9.86	3.919	2.576

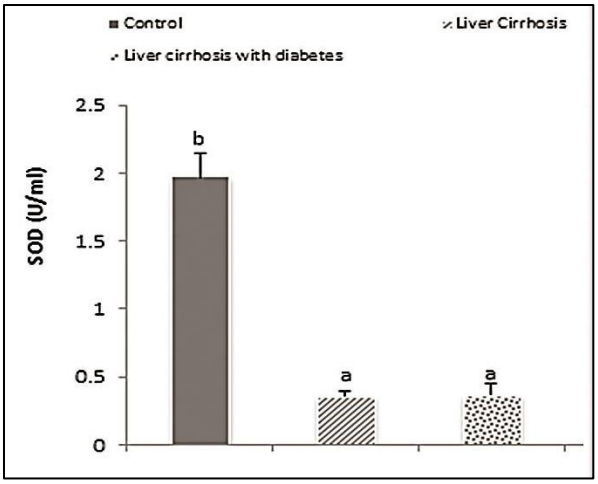

Figure 9: Serum super oxide mutes (SOD) among different groups

Serum super oxide mutes (SOD) in control group is (1.96 ± 0.17), in liver cirrhosis group (0.36 ± 0.04) and in liver cirrhosis with diabetes mellitus group (0.37 ± 0.08).

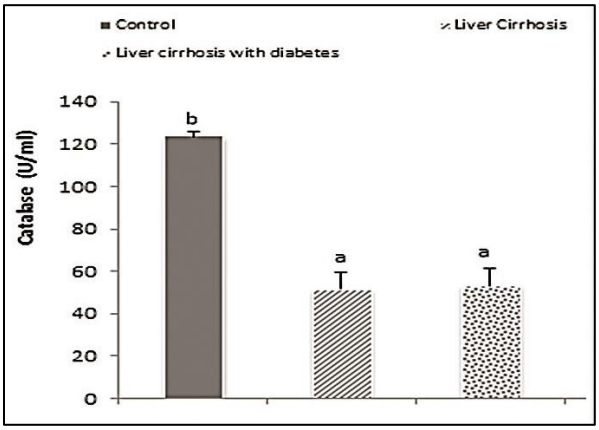

Figure 10: Catalase (CAT) concentration among different groups

Serum Catalase (CAT) in control group is (123.61 ± 2.12), in liver cirrhosis group (51.81 ± 7.75) and liver cirrhosis with diabetes mellitus group (53.39 ± 8.04).

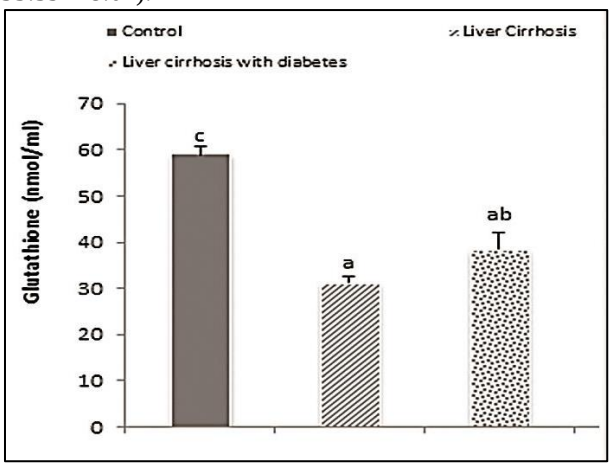

Figure 11: Glutathione (GSH) concentration among different groups

Serum Glutathione (GSH) concentration in control group was (59 ± 1.88), there was a significant decrease in liver cirrhosis group (31.29 ± 1.25), liver cirrhosis with diabetes mellitus group (38.45 ± 3.62). Also in our study there is

a significant increase in Lipid Peroxide Level MDA in all groups compared to healthy control. Thus, serum Malondialdhyde (MDA) concentration in control group was 2.15 ± 0.48 then significant decreased in liver cirrhosis with diabetes mellitus group to 9.79 ± 1.08) and in liver cirrhosis group at 11.52 ± 0.53 (Table 3 and Figure 12). This suggests that by increasing oxidative stress, there is corresponding proportionate decrease in antioxidant defense system. This fact was substantiated by negative correlation observed between MDA and GSH. This reflects that antioxidant defense system is compromised with increased free radical generation during hepatic damage. Lipid peroxidation has been shown to be a causative factor in the development of hepatic fibrosis. Malondialdehyde (MDA), a product of lipid peroxidation, can increase collagen production by activated hepatic stellate cells.

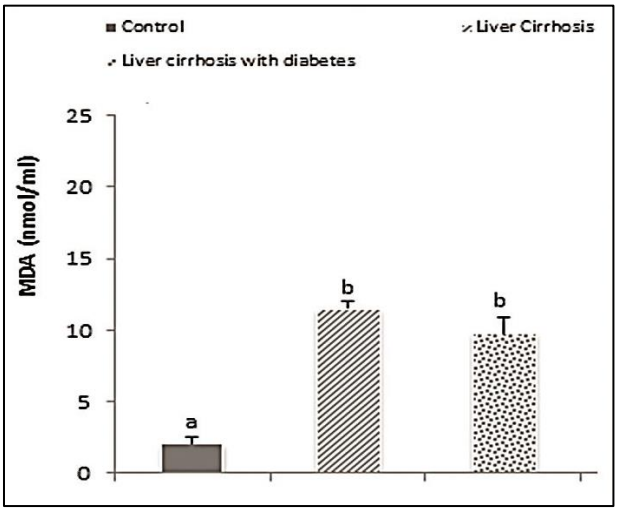

Figure 12: Malondialdhyde (MDA) concentration among different groups

Serum Malondialdhyde (MDA) in control group was (2.15 ± 0.48), liver cirrhosis with diabetes mellitus group (9.79 ± 1.08) and in liver cirrhosis group (11.52 ± 0.53). It should be noted that estradiol is a potent endogenous antioxidant and that antioxidant enzymes such as superoxide dismutase (SOD) provide a defense system.

CONCLUSION

Diabetic mellitus (DM) worsens the clinical course of liver cirrhosis. That DM accelerates liver fibrosis and inflammation giving rise to more severe liver failure and may potentiate the incidence of bacterial infections in cirrhotic patients which are associated with increased mortality that appeared in all biochemical parameters.

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