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Estimation Of Plasminogen Activator Inhibitor -1 And Some Biochemical Markers In A Sample Of Iraqi Patients With Liver Cirrhosis

Wassan Abdul Kareem, Baydaa Hameed Abdullah, Huda Jaber Waheed

Mustansiriyah University, Collage of Pharmacy .
Correspondent author: Wassan Abdul Kareem, Clinical Laboratory Science Department, College of pharmacy, Mustansiriyah University, Email: kamalfalcon97@yahoo.com

ABSTRACT

Objective: The aim of present study was designed to estimate level of plasminogen activator inhibitor -1 in liver cirrhotic patients, and its correlation with some biomarkers includes (Liver enzymes: ALT,AST and Bilirubin ,Total protein, albumin. Methods: The current study include 30 Iraqi liver cirrhotic patients with age range 25-65 years and 30 healthy control subjects with age range 25-60 years. Results: The present study had been shown a high significant differences in liver enzymes ALT, AST and ALP when compare with control p≤ 0.01, 0.05 and 0.01 respectively. The difference in the mean serum level of albumin and total bilirubin were also observed to be highly significant in the liver cirrhosis patients p ≤ 0.01. Concerning mean serum level of PAI-1 in the liver cirrhosis patients a significant deference was found when compared to control with p≤0.05. Also there were a non-significant correlation between age and studied parameters Conclusions: The results of the present study showed a significant increase in serum levels of PAI-1 ALT,AST,ALP,T Bilirubin ,and Albumin while a non-significant differences in these parameters was shown in relation to age and gender.

Keywords: liver cirrhosis, plasminogen activator inhibitor -1

Correspondence:
Wassan Abdul Kareem
Mustansiriyah University, Collage of Pharmacy .

*Corresponding author: Wassan Abdul Kareem email-address:
kamalfalcon97@yahoo.com

INTRODUCTION

It was considered that Cirrhosis is the final stage of chronic liver disease. It lead to distribution of the hepatic structure by fibrosis, and the formation of nodules (1). It is the result of advanced liver fibrosis caused by chronic liver disorders, including viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis (NASH), autoimmune liver disease, and genetic disorders. Recent studies support that the first stages of cirrhosis are reversible on a microscopic level with good treatment of the underlying liver disease(2), However, at progrresive stages, cirrhosis is thought irreversible. a variety of complications are due to cirrhosis, which lead to a reduction in the patients life (3) .At this stage, the only curative treatment is liver transplantation (4) .

Cirrhosis is the eighth cause that leads to of death and is responsible for 1.2% of all deaths in the USA (5). The worldwide cirrhosis prevalence is increasing according to the Global Burden of Disease study, (6). Chronic hepatitis C virus (HCV), alcoholic liver disease, and non-alcoholic liver disease , are the most common causes of cirrhosis in the USA (7). Unfortunately the incidence of the disease remains constant or is elevated in several countries, including both the UK and Ireland (8).

The most common causes in developed countries are alcoholic liver disease and hepatitis C , while in parts of Asia and in sub- Saharan Africa, hepatitis B is the most common cause(9).

Genetic predisposition to cirrhosis may explain the variable rates of its development in people with similar risk factors (like hepatitis C infection or alcohol abuse)(9). Vague symptoms like fatigue, malaise, anorexia, nausea and weight loss are seen in cirrhosis .In progressed liver disease, may include: Oedema, Ascites , Easy bruising , Poor concentration and memory, Bleeding oesophageal varices , Spontaneous bacterial peritonitis ,jaundice, scratch marks secondary to pruritus, spiderangiomata (naevi) ,skin telangiectasias ,palmar erythema, bruising,hair loss. . Hepatomegaly and a nodular liver are due to the direct alcohol toxic effect of in alcoholic cirrhosis or iron in haemochromatosis. Routine evaluation includes measurement of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and bilirubin.These tests are indirect markers of hepatobiliary disease or liver injury .In patients presenting with an isolated alkaline phosphatase elevation, measurement of the serum gamma-glutamyltransferase (GGT) level confirm cholestatic injury in which alkaline phosphatase is increased to differentiate liver from other organ sources. GGT should not be measured as a screening test for liver disease in the absence of abnormal liver disorders (10).

To assess the relative contribution of conjugated and unconjugated bilirubin fractions , total serum bilirubin should be fractionated; a rised serum conjugated bilirubin level implies hepatocellular disease or biliary obstruction. Initial screening test may help to establish whether liver function is impaired (coagulopathy or hypoalbuminemia) (11,12). Plasminogen activator inhibitor-1 (PAI-1) is a serine proteinase inhibitor and the primary inhibitor of the endogenous fibrinolytic system. It plays a key role in a wide range of physiological and pathological processes, including fibrinolysis, coagulation inflammation and wound healing (13). During inflammation Plasminogen activator inhibitor1 (PAI-1) which an acute phase protein can be induced (14, 15, 16). Both tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA)are inhibited by PAI-1 , so considered as a regulator of fibrinolysis (17). Plasmin also can degrade other ECM components such as laminin, proteoglycan, and type IV collagen (18,19,20). Also Plasmin can indirectly degrade ECM by stimulation of matrix metalloproteinases (MMPs) (21).

PAI-1 can change organ fibrogenesis by impairing the plasminogen activating systems. PAI-1 induction can be prevented pharmacologicaly and/or geneticlly and has been seen in models of renal, pulmonary, and vascular fibrosis (22, 23, 24). In hepatic fibrosis models PAI-1can be induced (25, 26). Recently it was found that PAI-1-deficient mice are protected from fibrosis (27).

The Aim of the present study is to estimation the PAI-1 levels in liver cirrhosis patients and to study the effect of age and gender on PAI-1 and some biochemical parameters in liver cirrhosis patients.

MATERIALS AND METHODS

This study was performed on 30 patients with liver cirrhosis and 30 healthy subjects as control (males and females).The samples of the patients were collected from Baghdad, Iraq at the period from December 2017 to June 2018. PAI-1 was assayed using enzyme linked immune sorbent assay ELISA Ray Bio Tech Co. USA.ALT,AST, ALP ,Total protein ,Total bilirubin, Albumin was assayed using Spectrophotometer Spain React Co. The patients included in this study were males and females within the age range of (25-65 years) without other diseases live in the city .

Statistical Analysis

SAS (2012) Statistical Analysis System- program was used to calculate the difference factors in study parameters . T-Test was used to obtain the significant comparison between means. Correlation coefficient between variables is estimated of in this study (28).

RESULTS AND DISCUSSION

The present study found that the difference in the mean serum level of liver enzymes(ALT , AST and ALP) in liver cirrhosis patients (43.90 ± 4.74 , 40.40 ± 3.20 and73.00 ± 4.78) respectively were very highly significant when compared to control (28.06 ± 1.30, 34.97 ± 1.05 and 57.70 ± 2.41) respectively with p ≤ 0.01 ,0.05,0.01 respectively as shown in table 1.

While the difference in the mean serum level of total protein was non significant between liver cirrhosis patients and control .The difference in the mean serum level of albumin and total bilirubin were also observed to be highly significant in the liver cirrhosis patients (3.48 ± 0.16 , 2.783 ± 0.24) respectively compare to control (4.49 ± 0.06 , 0.773 ± 0.02) respectively with p ≤0.01) as described in table 2. Concerning mean serum level of PAI-1 in the liver cirrhosis patients (58.69 ± 3.25) a significant deference was found when compared to control (50.59 ± 2.90) with p≤0.05 as reported in table 3. Table 4 show a non significant deference in the mean serum levels of the studied parameters between male and female . A non significant correlation were found between age of liver cirrhosis patients and studied parameters as shown in table 5.

In response to hepatocyte damage or death AST and ALT enzymes are released into the blood stream . The most common abnormality seen in liver blood test profiles is increase in these enzymes . In the present study it was found that both enzymes ALT and AST levels were significantly increased in liver cirrhosis The more liver-specific enzyme is ALT since it is present in low concentrations in non-hepatic tissue, and are uncommon. non-liver related elevations . The more specific indicator of liver disease is ALT ,but the concentration of AST may be a more sensitive indicator of liver injury in conditions such as autoimmune hepatitis (AIH) ,and alcohol-related liver disease . 29

The reticuloendothelial system produce by-product of haem breakdown which is component of haemoglobin by the reticuloendothelial system.30. In this study total bilirubin was highly significantly higher in liver cirrhosis patients than control . Bilirubin exists in two forms, unconjugated and conjugated. Itis transported to the liver in its insoluble unconjugated form, in order to be excreted it is converted into soluble conjugated bilirubin . Haemolysis or impairedconjugation lead to Unconjugated hyperbilirubinaemia while conjugated hyperbilirubinaemia is caused by parenchymal liver disease or obstruction of the biliary system. Total bilirubin will routinely reported in most laboratories ,which include unconjugated and conjugated fractions, therefor rise of either fraction will lead to a elevation in the measured bilirubin concentration,so an isolated elevated bilirubin concentration is found in Gilbert's syndrome, which is an inherited disease of metabolism and leads to reduce conjugation by impairing the activity of the enzyme glucuronyltransferase (31). The majority of measurable bilirubin should be conjugated Except in the neonatal period , even in individuals with advanced liver disease. If the majority of the elevated bilirubin comprises the unconjugated fraction then the cause, in the absence of haemolysis, is definitely Gilbert's syndrome. As Gilbert's syndrome is not related with liver disease or sickness, any such individuals should be fully screened.32

Albumin has multiple biological actions, such as maintenance of oncotic pressure, binding of other substances (such as fatty acids, bilirubin, thyroid hormone and drugs), metabolism of compounds, like lipids, and antioxidant properties ,and it is only produced by the liver, the synthetic function of the liver is measured by serum albumin concentration. However, the consideration of albumin as a marker of the liver disease severity is not always dependent,so in liver diseases albumin concentrations are reduced (33)

Table 1 . Compare between patients and control in level of liver enzymes

Mean ± SE			Group
ALP (IU/L)	AST (IU/L)	ALT (IU/L)	
73.00 ± 4.78	40.40 ± 3.20	43.90 ± 4.74	Patients
57.70 ± 2.41	34.97 ± 1.05	28.06 ± 1.30	Control
10.796 **	4.745 *	9.844 **	T-Test
0.0063	0.0412	0.0021	P-value
* (P<0.05), ** (P<0.01).			

Table 2 . Compare between patients and control in Total protein, Albumin and Total Bilirubin

Mean ± SE			Group
Total Bilirubin (mg/dl)	Albumin (g/dl)	Total protein (g/dl)	
2.783 ± 0.24	3.48 ± 0.16	6.98 ± 0.09	Patients

0.773 ± 0.02	4.49 ± 0.06	7.17 ± 0.09	Control
0.491 **	0.354 **	0.261 NS	T-Test

Table 3. Compare between patients and control in PAI-1 levels.

Mean ± SE	Group
PAI-1 (ng/mL)	
58.69 ± 3.25	Patients
50.59 ± 2.90	Control
6.731 *	T-Test
0.0487	P-value

Table 5. Correlation coefficient between age, and parameters of patients

Correlation coefficient-r with age		Parameters
Level of sig.	Correlation coefficient	
NS	-0.07	ALT
NS	0.02	AST
NS	-0.06	ALP
NS	-0.13	Total protein
NS	-0.04	Albumin
NS	0.14	Total Bilirubin
NS	-0.01	PAI-1
NS: Non-Significant.		

Table 4. Effect of gender in parameters of patients

T-Test	Mean ± SE		Parameters
	Female	Male	
20.20 NS	40.53 ± 5.18	49.73 ± 9.42	ALT (IU/L)
13.85 NS	40.21 ± 4.35	40.73 ± 4.69	AST (IU/L)
20.60 NS	74.79 ± 7.08	69.91 ± 4.84	ALP (IU/L)
0.391 NS	7.08 ± 0.10	6.82 ± 0.17	Total protein (g/dl)
0.709 NS	3.51 ± 0.20	3.42 ± 0.29	Albumin (g/dl)
1.056 NS	2.82 ± 0.32	2.71 ± 0.39	Total Bilirubin (g/dl)
14.03 NS	57.63 ± 3.84	60.52 ± 6.09	PAI-1 (ng/mL)

The classical role of (PAI-1) is inhibiting of plasminogen activators, therefore in alcoholic cirrhosis increased fibrinolysis is common ,decreased fibrinolysis driven mostly by increasing levels of PAI-1 that always occur during the development of liver disease, However, it was unclear whether or not PAI-1 plays a causal role in the development of early liver disease. Experimental models in Recent studies have suggested that PAI-1 may lead to early (steatosis) , it suggests that PAI-1 plays a critical role in hepatic disease (34).

CONCLUSION

The results of the present study showed a significant increase in serum levels of PAI-1 ALT,AST,ALP,T Bilirubin ,and Albumin while a non significant differences in these parameters was shown in relation to age and gender , inflammation, fibrin accumulation may be due to its ability which subsequently sensitizes the liver to produce damaging insults, in hepatic fibrosis the role of PAI-1 is less clear and appears that PAI-1 may serve two roles in this defect , both enhancing regeneration (protective) and blocking matrix degradation (damaging)(35) .Concerning the effect of gender on the studied parameters there were a non significant effect of gender on these parameters , also there were a non significant effect of age on the studied parameters .

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