Evaluation the Diagnostic Values of Direct and Indirect Non-invasive Biochemical Markers of Liver Fibrosis in Patients with Chronic Hepatitis B Virus

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Abstract. To investigate hepatic fibrosis in chronic hepatitis B patients using non-invasive direct and indirect biomarkers, as well as to assess the diagnostic accuracy of these biomarkers. There are 119 people in a case-control study: 50 healthy people served as controls, whereas 69 individuals with chronic hepatitis B were diagnosed using the PCR method. In addition to cholesterol, the direct biomarkers (serum fibronectin, haptoglobin, and TNF alpha) and indirect biomarkers (serum total bilirubin, direct bilirubin, aspartate aminotransferase AST, alanine aminotransferase ALT, alkaline phosphatase ALP, albumin, and gamma-glutamyl transferase - GGT) are For liver function tests and a fibrotic marker, there was a significant difference ($P < 0.05$) between control and HBV patients: fibronectin (168.56± 98.47 control vs. 98.24 ± 74.87 HBV) and TNF alpha (121.96+124.8 control vs. 56.03±48.39 HBV). The haptoglobin and cholesterol revealed no differences between males or females when compared with control. The sensitivity of fibrotic markers: fibronectin, TNF alpha, and haptoglobin cannot be calculated. These biomarkers could be used instead of a liver biopsy to track the progression and therapy of liver fibrosis.

Keywords: Hepatitis B virus, liver fibrosis, Liver Biopsy.

1 Introduction

The creation of an excessive quantity of scar tissue in the liver is known as hepatic fibrosis. It occurs when the liver strives to repair and replace damaged cells. The liver can be injured by a variety of factors. Fibrosis itself causes no symptoms, but severe scarring can lead to cirrhosis. The persistence of liver viral infection causes chronic damage and excessive extracellular matrix formation by hepatic stellate cells in the liver, which can lead to cirrhosis and malignancy. The liver is a multilobed reddish-brown glandular organ that occupies most of the upper right section of the human abdominal cavity, just below the diaphragm. It is in charge of metabolism, immunity, digestion, detoxification, and storage, among other things [1]. It also has the responsibility of regulating the flow and safety of substances absorbed from the digestive system prior to their distribution to the systemic circulatory system. The importance of the liver is reflected by the fact that complete loss of hepatic function can result in death within minutes [2]. Hepatitis is an inflammation of the liver which results in damage to hepatocytes with subsequent cell death (necrosis) [3]. Liver fibrosis is a complicated fibrogenic and inflammatory process that develops as a result of chronic liver injury and is a precursor to liver cirrhosis [4].

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2 Materials and Methods

119 participants took part in the case-control study: 50 healthy controls (26 men and 24 women) and 69 patients with chronic hepatitis type B for at least 6 months (36 males and 33 females). Al-Faiha'a Gastrointestinal Centre in Barah, Iraq, treated the patients. Full clinical examinations and laboratory tests were used to diagnose the patients. The Patients, who had chronic diseases except for patients in our study were excluded from the study. The parameters Haptoglobin is the measurement by Abbott C4000 autoanalyzer. The ELISA technique was used to measure fibronectin and TNF alpha. Cobas INTEGRA plus 400 auto analysers for liver function testing and cholesterol measurement.

2.1 Statistical Analysis

Statistical significance was defined as p-values less than 0.05 using IBM SPSS Statistics 22.0.

3 Results

3.1 Control and Hepatitis B Patients

This work was observed that the age, sex, and haptoglobin did not show statistical differences between the control group and hepatitis B patients (P-value >0.05), While all the other variables were shown significant differences (P <0.05) as represented in Table 1.

Table 1. Data on healthy people and individuals with hepatitis B.

Variables		Control (N= 50)	Hepatitis B (N= 69)	P-Value
Age		42.2 ± 15.7	43.0 ± 15.9	0.784
Sex	Male	36 (52.2%)	26 (52.0%)	0.912
	Female	33 (47.8%)	24 (48.0%)	
	Total	69 (100%)	50 (100%)	
Bilirubin- T		0.41 ± 0.17	2.58 ± 2.27	0.0001
AST		16.24 ± 4.61	60.37 ± 56.11	0.0003
ALT		29.90 ± 10.26	74.73 ±71.5	0.0002
ALP		75.12 ± 15.09	115.4 ± 73.78	0.0001
GGT		17.65 ± 7.81	88.19 ± 83.06	0.0001
Albumin		4.28 ± 0.24	4.11 ± 0.51	0.001
Haptoglobin		156.20 ± 54.33	159.82 ± 59.09	0.731
Fibronectin		168.56 ± 98.47	98.24 ± 74.87	0.0001
TNF		121.96 ± 124.83	56.03 ± 48.39	0.0001

3.2 Comparison Between Control and Hepatitis B Patients According to Gender

Table 2 shows the gender contrast between control and hepatitis B patients. In the current study, all variables (P <0.05) in male and female patients with hepatitis B were substantially different from the control group, with the exception of haptoglobin (P > 0.05).

Table 2. Control and hepatitis B patients data according to sex.

Variables	Males			Females		
	Control (N= 26)	Hep. B (N = 36)	P. Value	Control (N = 24)	Hep. B (N = 33)	P. Value
Bilirubin-T	0.47 ± 0.13	2.61 ± 2.32	0.0001	0.35 ± 0.18	2.55 ± 2.25	0.0001
AST	17.98 ± 4.79	57.20 ±49.9	0.005	14.36 ± 3.65	63.81 ±62.7	0.007
ALT	32.80 ± 9.79	85.05 ± 83.9	0.0003	26.88± 10.06	63.48 ± 53.9	0.0045
ALP	74.07 ± 14.80	108.13 ±82	0.012	76.25 ± 16.85	123.49 ± 63	0.001
GGT	21.88 ± 8.08	73.13 ± 69.3	0.0003	13.06 ± 4.2	74.21 ± 67.8	0.001
Albumin	4.38 ± 0.18	4.23 ± 0.48	0.032	4.37 ± 0.3	3.99 ± 0.53	0.001
Haptoglobin	162.84 ± 46.64	150.22 ± 49	0.830	149 ± 61.81	170.3 ± 67.2	0.645
Fibronectin	120.47 ±101.16	68.9 ± 70.14	0.0001	220.66 ± 63.93	130.25 ± 67.13	0.001
TNF	72.84 ± 67.88	48.67 ± 31.87	0.004	175.16 ± 150.	64.06 ± 61.13	0.002

3.3 ROC Analysis for the Hepatitis B

Table 3 shows the ROC for the identification of liver fibrosis in hepatitis B. According to the findings of this investigation, fibronectin and TNF had the lowest AUC.

Table 3. ROC for liver fibrosis detection with hepatitis B.

Variables	The area under the ROC curve	p-value (AUC0=0.5)	Best cut-off criterion	Sensitivity (%)	Specificity (%)	Efficiency	PPV	NPV
Haptoglobin	0.519	0.772	-	-	-	-	-	-
Fibronectin	0.278	0.0001				-	-	-
TNF	0.374	0.020	-	-	-	-	-	-

3.4 Identification of people with hepatitis B

According to the findings of this investigation, no parameters had statistically significant differences (P>0.05). The size of the odds ratios, on the other hand, differed. Table 4 shows that GGT and AST were optimum.

Table 4. Detail of people with hepatitis B who are at risk of developing liver fibrosis.

Variables	P. Value	Odd ratio	95% Confidence Limits	
			Low	Upper
Bilirubin T	0.917	0.0001	0.0001	*
AST	0.966	11.781	0.0001	66.0
ALT	0.933	0.028	0.0001	1.790
ALP	0.967	0.545	0.0001	12.000
GGT	0.959	20.141	0.0001	3.400
Albumin	0.999	0.080	0.0001	*
Haptoglobin	0.930	1.939	0.0001	511.000
Fibronectin	0.931	0.579	0.0001	12.000
TNF	0.944	1.389	0.0001	130.0

3. 5 Correlations Patients Results

Table 5 shows the associations between the factors for patients. A correlation coefficient of 0.6 or higher was regarded significant in this study as an indicator of correlation between binary variables. All other factors were not significant except for ALT and AST.

Table 5. Correlations over patients.

	Bilirubin D	AST	ALT	ALP	GGT	Albumin	Hepato.	Fibronectin	TNF	Cholesterol
Bilirubin T	**0.92**	**0.461**	**0.581**	**0.401**	**0.221**	**0.251**	**0.06**	**0.081**	**0.071**	**0.16**
AST		**1**	**0.631**	**0.381**	**0.401**	**0.151**	**0.02**	**0.131**	**0.101**	**0.08**
ALT			**1**	**0.351**	**0.311**	**0.151**	**0.04**	**0.081**	**0.071**	**0.13**
ALP				**1**	**0.521**	**0.401**	**0.03**	**0.091**	**0.061**	**0.12**
GGT					**1**	**0.361**	**0.01**	**0.171**	**0.121**	**0.09**
Albumin						**1**	**0.08**	**0.101**	**0.091**	**0.01**
Hepato.							**1**	**0.061**	**0.021**	**0.01**
Fibronectin								**1**	**0.721**	**0.12**
TNF									**1**	**0.02**

4 Discussion

The deposition of ECM produced by HSC and other hepatic cells is directly involved in liver fibrosis markers, as well as indirect liver function assessments. Hepatic injury is linked to a disruption of several metabolic activities, that helps with the biochemical analysis of liver illness. The current study revealed the haptoglobin in HBV patients (159.82) was a non-significant difference when compared with control, this result appeared due to begin to decrease the haptoglobin concentration after it was elevated at the onset of infection because

of the progress of hepatocyte damage and synthesis of fibrosis this result was an agreement with [5]. The fibronectin levels in hepatitis B were significant low (98.24) compared with control, the decreased level of fibronectin due to decrease releasing from hepatocytes in patients with chronic hepatitis this result was an agreement with [6], the fibronectin serum level increases with the advancement of liver fibrosis but finally decreases in patients with cirrhosis due to hepatic dysfunction which agreement with [7] and [8]. In dendritic cells, the viral core proteins induce immunological tolerance and overproduce IL-10, which can suppress the production of pro-inflammatory cytokines. The viral core proteins, which induce immunological tolerance in dendritic cells and overproduce IL-10, which can suppress the production of pro-inflammatory cytokines, appeared to be responsible for this result (TNF-α). The result was an agreement with [9]. The current study revealed the mean of haptoglobin, fibronectin, and TNF alpha in the male (150.22, 68.9, 48.67) respectively lower than female this indicter the liver fibrosis in the male more progress than female, this result agreement with [10]. Estrogens are important for preserving homeostasis and making the liver less vulnerable to a variety of chronic liver disorders, according to [11]. Feminine immune responses are greater than male immune responses in adulthood, which resulting in a decreased risk of infection and a superior ability to clear viral infection in women, according to [12]. ROC curves are used to diagnose liver fibrosis caused by hepatitis B. The results showed that haptoglobin, fibronectin, and TNF had an area under the ROC less than 0.6, therefore sensitivity and specificity could not be calculated. The risk of liver fibrosis was determined using multivariable logistic regression analysis. The outcomes were shown that some variables in the model were non-significant(P value>0.05), but the odds ratios in these parameters are more risk compared with other parameters, this result is an agreement with [13].

4 Conclusion

Hepatic fibrosis can be predicted directly and indirectly using direct and non-invasive biochemical markers in patients with chronic hepatitis B virus, as well as the progression and management of fibrosis.

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