Original Article

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Biochemistry Section

Serum Basal Paraoxonase 1 Activity as an Additional Liver Function Test for the Evaluation of Patients with Chronic Hepatitis

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ABSTRACT

Background: The diagnostic accuracy of currently available standard panel of liver function tests is not satisfactory for the reliable diagnosis of chronic liver disorders. Earlier studies have reported that serum basal paraoxonase 1 (PON1) activity measurement may add a significant contribution to the liver function tests.

Aim: To assess whether the measurement of serum basal paraoxonase 1 (PON1) activity would be useful as an index of liver function status in chronic hepatitis patients.

Materials and Methods: The study included 50 chronic hepatitis patients and 50 apparently healthy controls based on inclusion & exclusion criteria. In all the subjects, standard liver function tests were analysed by using standard methods. Basal PON1 activity was estimated using spectrophotometric method by the hydrolysis of p-nitrophenylacetate. Student t-test, Pearson's correlation coefficient, diagnostic validity tests and ROC curve analysis were the methods used for the statistical analysis of the data.

Results: The serum basal PON1 activity was significantly decreased in chronic hepatitis cases when compared to controls ($p< 0.001$). Also basal PON1 activity was positively correlated with serum total protein and albumin, and negatively correlated with serum total bilirubin, alanine amino transferase (ALT), and alkaline phosphatase (ALP) ($p< 0.001$) in chronic hepatitis cases but not in healthy controls. Diagnostic validity tests showed, basal PON1 activity was a better discriminator of chronic hepatitis than total protein, albumin and ALP with sensitivity of 68%, specificity of 100%, positive predictive value of 100% and negative predictive value of 75%. ROC curve analysis demonstrated highest diagnostic accuracy for ALT (AUC = 0.999) followed by PON1 (AUC = 0.990), total bilirubin (AUC = 0.977), ALP (AUC = 0.904), total protein (AUC = 0.790) and albumin (AUC = 0.595).

Conclusion: Diagnostic accuracy of serum PON1 activity is better than total bilirubin, total protein, albumin and ALP. PON1 activity measurement could significantly improve the current efficiency of a laboratory's evaluation of patients with suspected chronic hepatitis.

Keywords: Alanine transaminase, Albumin, Alkaline phosphatase, Bilirubin, Chronic, Hepatitis, Human, PON1 protein

INTRODUCTION

Chronic hepatitis includes a group of liver disorders of varying causes and severity in which the hepatic inflammation and necrosis lasts for more than six months. Severity of the disease may vary from milder forms in which the progression is very slow and may go undetected for a long time, to more severe forms which are associated with the parenchymal scarring and structural disorganization leading to cirrhosis [1]. Chronic liver disease and cirrhosis are the 10th leading cause of mortality. Among the various causes, Hepatitis C Virus (HCV) infection is the most frequent cause of chronic hepatitis. A 75 to 80 percent of persons with HCV infection develop chronic hepatitis, and a more than 25 percent develop cirrhosis within 30 to 40 years. It has been estimated that, up to 25 percent of cirrhotic patients will eventually succumb to their liver disease [2]. Hepatitis B is another major cause of chronic liver disease. Infection with hepatitis B virus (HBV) is a major cause of morbidity and mortality in the South East Asian Region (SEAR). More than one third of the population has been infected and approximately 2 lakhs deaths occur in this region due to HBV infection [3].

Chronic liver diseases are slow progressive diseases. The progression is subtle, and the liver function tests often remain within the laboratory reference values until gross disease becomes evident. To diagnose such a slow progressive liver diseases before advancing to hepato-cellular necrosis and fibrosis, beside traditional biochemical tests needs alternative parameters to evaluate liver damage [4].

Currently it is widely accepted that the sensitivities of standard biochemical tests for liver function are low and insufficient for a reliable determination of the presence or absence of liver disease [4]. Histo-pathological examination of liver biopsy sample is considered as the best method for the diagnosis of the parenchymal liver disease such as chronic hepatitis. However, liver biopsy is essentially an invasive procedure with certain unavoidable complications. Hence, a reliable, accurate and non-invasive hepatic biomarker is the need of the hour [5].

Paraoxonase (PON1) is a aryldialkylphosphatase which catalyzes the calcium dependent hydrolysis of many xenobiotics [6], such as many OP compounds including paraoxon (from which it takes its name), the insecticides parathion and chlorpyriphos, nerve agents sarin and soman; arylesters like phenylacetate, as well as aliphatic lactones such as dihydrocoumarin, γ-butyrolactone and homocysteine thiolactone [7].

In humans, PON comprises a family of three enzymes which includes PON1, PON2 and PON3, whose genes are located on chromosome 7q21-22 [8]. Paraoxonase 1 (PON1) is a glycoprotein, containing 355 amino acids [7], with a molecular mass of 43-45 kDa. PON1 is synthesized mainly by the liver. After synthesis, some of the PON remains inside the hepatocyte, and some of it is released into the blood where it binds to High Density Lipoprotein (HDL) by association with apolipoprotein A1 [6].

Oxidative stress is implicated in the pathogenesis of various liver disorders [9]. Oxidative stress is involved in the patho-physiology of

alcoholic liver disease, non-alcoholic steatohepatitis and hepatitis C virus infection, which ultimately can lead to the development of liver cirrhosis and hepatocellular carcinoma [10]. PON1 protects against the oxidative stress by the inhibition of lipid peroxidation. Hence there can be a possible relationship between PON1 and oxidative stress in liver diseases [11]. Earlier studies have observed a significant decrease of serum PON1 activity in patients with chronic hepatitis [12-14].

In view of these observations, in this study we compared the serum PON1 activity and the standard liver function tests (serum total bilirubin, total proteins, albumin, alanine aminotransferase and alkaline phosphatase) between chronic hepatitis patients and healthy controls, to investigate possible application of its measurement in serum for an improved evaluation of hepatic function.

MATERIALS AND METHODS

A cross-sectional study of standard liver function tests and basal paraoxonase 1 (PON1) activity was carried out in chronic hepatitis patients and healthy controls. Each participant gave an informed consent and this study was approved by the Institutional Ethical and Research Committee. The procedures followed were in accordance with the Helsinki Declaration of 1975 that was revised in 2000.

Based on inclusion and exclusion criteria, 50 chronic hepatitis cases and 50 age and sex matched healthy controls were included in the study. Chronic hepatitis cases were diagnosed by the attending physician depending on [1,15] the history (history of ethnic origin from a high carrier rate country, sexual contacts, contact with human blood, transplants, immunosuppressive treatment, drug abusers and homosexuals or intake of certain drugs like oxyphenisatin, α-methyldopa, nitrofurantoin, papaverine, dantrolene, clometacine, ticrynafen, isoniazid (INH), propylthiouracil and sulfonamide, etc.), clinical features (fatigue, anorexia, jaundice), standard liver function tests (elevated serum bilirubin, ALT, ALP and Hypoalbuminemia) and liver biopsy findings (perioportal necrosis/intralobular necrosis, portal inflammation and/or fibrosis). Subjects with diabetes mellitus, neoplasia, renal disease, cardiovascular disease and other infectious/inflammatory diseases were excluded from the study. From all the subjects, about 5 ml of blood sample was drawn under all aseptic precautions from a large peripheral vein and collected in a sterile plain bulb. The blood was allowed to clot for about 30 minutes and serum was separated by centrifugation at 5000 rpm and kept at 2-4°C until analysis was carried out.

The standard panel of liver function tests (serum total bilirubin, total proteins, albumin, alanine aminotransferase and alkaline phosphatase) were done by using the reagent kits (Merck Millipore Corporation, Darmstadt, Germany), in Microlab-300 semi-auto anaylser (ELITech Group, Puteaux, France) [16-20]. PON1 activity was determined by spectrophotometric method using p-nitrophenylacetate as a substrate [21]. The activity was measured at 25°C by adding 50 µL of serum to 3 mL of buffer containing 1 mM/L $CaCl_2$ in a spectrophotometric cuvette. The initial absorbance was adjusted to 0.500 in a spectrophotometer at a wavelength of 412 nm. The reaction was started by adding 50 µL of substrate. The rate of increase in absorbance was monitored at 30, 60, 90, 120 and 150 seconds. Non-enzymatic hydrolysis was done by adding 3 mL of buffer and 50 µL of substrate in a spectrophotometric cuvette. The rate of change in absorbance (A) was monitored at 30, 60, 90, 120 and 150 seconds at 412 nm. The ΔA so obtained was deducted from ΔA obtained in the presence of serum.

Calculation

Correction for non enzymatic hydrolysis: Corrected ΔA = Total ΔA – non enzymatic ΔA

PON1 activity was calculated by using molar extinction coefficient of 17000 M^{-1} cm^{-1}

= 0.017/nmol/cm/mL => 0.00567/nmol/3 mL (as total volume was 3 mL).

So enzyme activity per 50 µL of serum under assay conditions:

ΔA/min/0.00567 = ΔA/min × 176 U/mL (nmol/mL/min).

The ΔA for 2 min was taken from 30 to 150 seconds for calculating the enzymatic activity. The first 30 seconds was not taken for calculation in order to allow the reaction to reach a steady state.

Enzyme activity: PON1 activity is expressed as Units/mL of serum (nmol/mL/min), where 1 U = 1 nanomole of p-nitrophenol formed per minute.

ΔA in presence of $CaCl_2$ for basal activity is 0.011.

STATISTICAL ANALYSIS

Descriptive data are presented as mean±SD values. Differences between means of two groups were assessed by Student t-test. The Pearson's correlation coefficient was used to evaluate the degree of association between the two variables. Diagnostic validity tests and ROC curve analysis was done to assess the diagnostic accuracy of all the variables. A p-value of 0.05 or less is considered for statistical significance.

RESULTS

The study included 50 chronic hepatitis cases with a mean age of 41.8±9.8 years, and 50 healthy controls with a mean age of

Variable	Chronic hepatitis cases (n = 50) (Mean±SD)	Healthy Controls (n = 50) (Mean±SD)	p-value
Age (Years) (Mean±SD)	41.8 ± 9.8	45.6 ± 11.8	0.080
Males (%)	70	56	0.147
Females (%)	30	44	0.147
Total Bilirubin (mg/dL)	4.05 ± 1.74	0.74 ± 0.14	< 0.001
Total Protein (g/dL)	6.2 ± 0.34	6.83 ± 0.72	< 0.001
Albumin (g/dL)	3.54 ± 0.34	3.72 ± 0.55	0.35
ALT (U/L)	135.92 ± 41.86	21.18 ± 6.87	< 0.001
ALP (U/L)	164.98 ± 47.42	88.78 ± 35.48	< 0.001
Basal PON1 activity (nmol/mL/min)	101.88 ± 23.08	176.68 ± 25.88	< 0.001

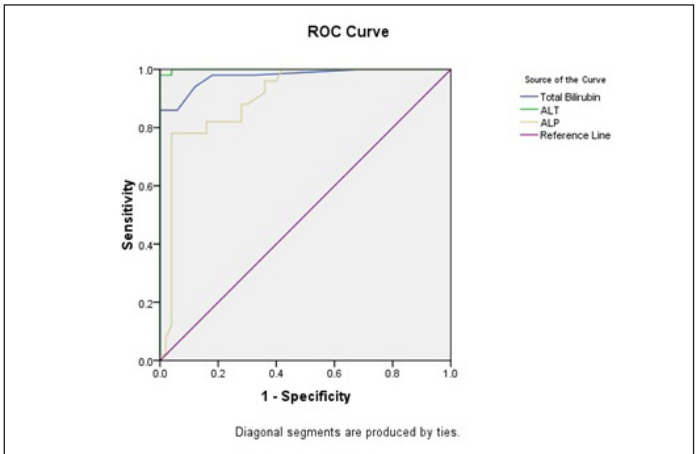
[Table/Fig-1]: Comparison of demographic variables, standard liver function tests and basal PON1 activity in chronic hepatitis cases and healthy controls
p < 0.001 = HS (highly significant), p > 0.05 = NS (not significant)

Variable	Basal PON1 activity			
	Controls		Chronic hepatitis	
	'r'	'p'	'r'	'p'
Total bilirubin	- 0.04	0.81	- 0.60	< 0.001
Total protein	- 0.03	0.85	0.59	< 0.01
Albumin	0.19	0.25	0.65	< 0.001
ALT	0.23	0.16	- 0.82	< 0.001
ALP	- 0.19	0.24	- 0.69	< 0.001

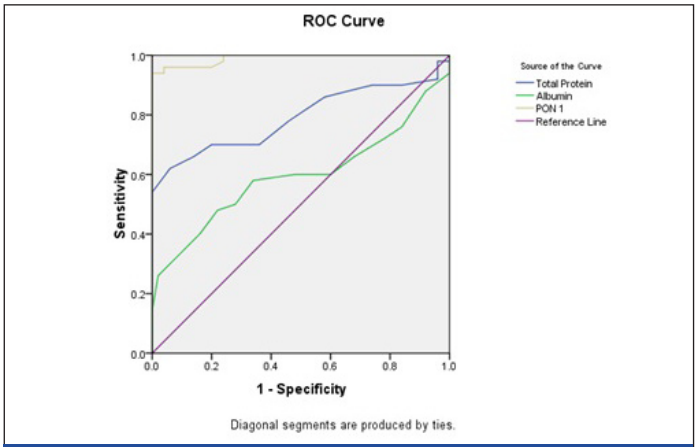
[Table/Fig-2]: Correlation between serum basal PON1 activity and standard liver function tests in chronic hepatitis cases and healthy controls
'r'= Pearson's correlation coefficient

Cut-off value	Total bilirubin > 1.0 mg/dL	Total protein < 6.0 g/dL	Albumin < 3.5 g/dL	ALT > 45.0 U/L	ALP > 125.0 U/L	Basal PON1 activity < 113.0 U/mL (nmol/mL/min)
Sensitivity (%)	86	18	40	98	72	68
Specificity (%)	94	90	60	100	96	100
PPV (%)	93	64	50	100	94	100
NPV (%)	87	52	50	98	77	75

[Table/Fig-3]: Diagnostic validity tests for serum total bilirubin, total protein, albumin, ALT, ALP, and basal PON1 activity for diagnosis of chronic hepatitis
PPV = Positive predictive value, NPV = Negative predictive value



[Table/Fig-4]: Diagnostic accuracy of serum total bilirubin, ALT and ALP in the diagnosis of chronic hepatitis



[Table/Fig-5]: Diagnostic accuracy of serum Total Protein, Albumin and PON1 activity in the diagnosis of chronic hepatitis

	AUC	p-value	Confidence Interval	
			Lower limit	Upper limit
Total bilirubin	0.977	< 0.001	0.951	1.002
Total protein	0.790	< 0.001	0.696	0.885
Albumin	0.595	0.101	0.479	0.711
ALT	0.999	< 0.001	0.997	1.001
ALP	0.904	< 0.001	0.841	0.967
Basal PON1 activity	0.990	< 0.001	0.976	1.004

[Table/Fig-6]: Area under ROC curve for basal PON1 activity and standard liver function tests

45.6±11.8 years. The incidence of chronic hepatitis was higher in males when compared to females.

[Table/Fig-1] shows comparative analysis of various standard liver function tests and serum basal PON1 activity between chronic hepatitis cases and healthy controls. The levels of serum total bilirubin, ALT, ALP are significantly increased and the levels of serum total protein, albumin, and basal PON1 activity are significantly decreased in patients with chronic hepatitis when compared to healthy controls and the difference was statistically significant ($p < 0.001$) except for albumin, which is decreased, but is not statistically significant ($p = 0.35$).

[Table/Fig-2] shows the Pearson's correlation between serum basal PON1 activity and serum total bilirubin, total protein, albumin, ALT and ALP in chronic hepatitis cases and healthy controls. It is evident from the table that serum total protein and albumin are positively correlated and the serum total bilirubin, ALT, and ALP are negatively correlated with serum basal PON1 activity in chronic hepatitis cases. This correlation is also statistically significant ($p < 0.001$). There is no such correlation between standard liver function tests and basal PON1 activity in healthy controls.

[Table/Fig-3] shows results of diagnostic validity tests in predicting disease for a given standard liver function tests and basal PON1 activity level. Here the validity tests are done to discriminate between chronic hepatitis cases and controls. Standard laboratory reference values are used as cut off values for standard liver function tests and median for basal PON1 activity for discriminating chronic liver disease cases from controls.

It is evident from the table that basal PON1 activity is a better discriminator of chronic hepatitis than total protein, albumin and ALP with sensitivity of 68%, specificity of 100%, positive predictive value of 100% and negative predictive value of 75%. But total bilirubin and ALT are better discriminators of the disease than basal PON1 activity. [Table/Fig-4-6] shows the ROC curve analysis for all the study parameters. Among the study parameters, ALT demonstrated highest diagnostic accuracy (AUC=0.999) followed by PON1 (AUC=0.990), total bilirubin (AUC=0.977), ALP (AUC=0.904), total protein (AUC=0.790) and albumin (AUC=0.595).

DISCUSSION

Chronic liver diseases (chronic hepatitis and cirrhosis) are one of the most important diseases leading to high morbidity and mortality. Worldwide, an estimated 300–350 million individuals (5–6% of the world population) are chronically infected with Hepatitis B Virus (HBV). An estimated 170 million individuals (3% of the world population) are chronically infected with Hepatitis C Virus (HCV) [22].

Majority of the biochemical and metabolic functions of the body takes place in the liver. In various liver disorders, these metabolic functions get adversely affected leading to the alteration in the levels of certain biochemical substances in the blood. Hepatic diseases can be diagnosed by measuring the concentrations of these biochemical analytes [23]. Oxidative stress is also involved in the patho-physiology of alcoholic liver disease, non-alcoholic steatohepatitis and hepatitis C virus infection, which ultimately can lead to the development of liver cirrhosis and hepatocellular carcinoma [24].

Apart from liver, PON1 activity has also been identified in various other tissues such as kidney, brain and lung. It has been studied extensively in cardiovascular diseases, whereas, there is a paucity of data with regard to the role of PON1 activity in liver diseases. After the synthesis, some portion of the PON1 is secreted into the circulation and remaining portion is stored in the liver. PON1 bound to HDL in the circulation, protects LDL from peroxidation. The probable function of PON1 in the liver is protection of the liver from the oxidative stress [14].

In the present study, the serum basal PON1 activity is significantly decreased ($p < 0.001$) in chronic hepatitis cases when compared to controls. This finding is in accordance with the findings of studies of Ferre et al., (2002), Ferre et al., (2005), Kilic et al., Baskol et al., Ferre et al., (2006), Aslan et al., Fei et al., and Ali et al., [12-14,25-29].

The decrease in the PON1 activity in chronic hepatitis patients can be explained by the following two mechanisms. Firstly, because PON1 is synthesized in the liver, hepatic injury in chronic hepatitis can impair its gene expression and/or activity [12]. This explanation can be supported by the observation that, in rats with chronically administered CCl_4, the PON1 activity gets inhibited due the hepatic injury caused by CCl_4 [30]. In the second mechanism, serum PON1 activity (with normal hepatic PON1 concentration) may get affected secondary to the alterations in the synthesis and/or secretion of HDL. Impaired synthesis and altered structure of HDL associated with the decrease in the hepatic LCAT activity are common in chronic liver diseases [12]. Recently, decrease in the serum PON1 activity has been observed in mice with LCAT deficiency due to the targeted disruption of LCAT gene [31].

Our results also show that, basal PON1 activity is positively correlated with serum total protein and albumin, and negatively correlated with serum total bilirubin, ALT, and ALP. This correlation

is also statistically significant (p< 0.001). There is no such correlation between standard liver function tests and basal PON1 activity in healthy controls. These results are consistent with the studies of Ferre et al., (2002), Ferre et al., (2005), Kilic et al.,, Fei et al.,, and Ali et al., [12-14,28,29]

According to the diagnostic validity test, basal PON1 activity is a better discriminator of chronic hepatitis than total protein, albumin, ALP with sensitivity of 68%, specificity of 100%, positive predictive value of 100% and negative predictive value of 75%. But total bilirubin and ALT are better discriminators of the disease than basal PON1 activity. ROC curve analysis demonstrated that, among the study parameters, ALT demonstrated highest diagnostic accuracy (AUC=0.999) followed by PON1 (AUC=0.990), total bilirubin (AUC=0.977), ALP (AUC=0.904), total protein (AUC=0.790) and albumin (AUC=0.595). These findings were similar to the study conducted by Ferre et al., (2002) [12].

These results demonstrate that serum PON1 activity measurement may add a significant contribution to liver function tests. Recent evidence indicates that HDL inhibits cell apoptosis and when HDL gets oxidized, it loses its capacity to inhibit the cell apoptosis. Hence, PON1 which is known to protect HDL from oxidation, would encourage the anti-apoptosis potential of HDL. These results suggest an active role of PON1 in the regulation of oxidative stress, fibrosis, and hepatic cell apoptosis in chronic liver diseases [24]. Further studies are required to gain further insight to this hypothesis. In another study, a genetic association between PON1192 polymorphism and chronic hepatitis C virus infection has been identified. However, the study warrants further investigation and their findings need to be confirmed in larger, independent cohorts [13].

LIMITATION

Relatively small sample size.

CONCLUSION

Serum PON1 activity is reduced significantly in patients with chronic hepatitis. Diagnostic accuracy of serum PON1 activity is better than total bilirubin, total protein and albumin and ALP. Measurement of PON1 activity can be an additional diagnostic test for the better evaluation of patients with chronic hepatitis.

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