Assessment of C-reactive protein titer in patients with chronic hepatitis B virus infection

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Abstract:

Background: C-reactive protein (CRP) is acute-phase reactant that is increased during inflammation, infection and tissue damage. CRP titer can be a useful marker for disease progression and effectiveness of treatment.

Objectives: To evaluate the serum C- reactive protein titer as a predictive marker for the diagnosis of chronic hepatitis B virus infection.

Patients and methods: one hundred and five patients with chronic HBV infection and 117 apparently healthy individuals as a control group were enrolled in the present study. The patients include 69 (65.7%) males with mean age 32.4 ± 11.8 years and 36 (34.3%) females with mean age 35.2 ±12.2 years. The control group includes 57(48.7%) females with mean age 23.2 ± 5.9 years and 60 (51.3%) males with mean age 28.7 ± 5.9 years. The diagnosis of chronic HBV infection was based on detection of HbsAg in the patient's sera. Assessment of CRP titer was done using semi-quantitative tube agglutination test. All data were statistically analyzed.

Results: Using the 95% percentile, the baseline CRP titer among healthy controls was 1/8 (16 mg/L), and for patients with chronic HBV infection was 1:32 (64 mg/L), with a statistically significant difference between the two groups (P<0.001). The validity of CRP titer at 1:16 as cut-off value was found to be reasonably sensitive (55%) and highly specific (96%) with a test accuracy of (77%) for differentiating between healthy controls and patients when the clinical suspicion was 50%.

Conclusion: When the clinical suspicion was 50%, the CRP titer at 1:16 may be of value as a predictive marker for differentiation between healthy individuals and patients with chronic HBV infection.

Keywords: chronic HBV infection, C-reactive protein, HBsAg.

Introduction:

C-reactive protein is a member of the class of acute-phase reactants. CRP is not normally found in the blood of healthy people,

It appears after an injury, infection, or inflammation and disappears when the injury heals or the infection or inflammation subside [1,2].

This increment is due to a rise in the plasma concentration of IL-6, which is produced predominantly by macrophages as well as adipocyte [3].

The amount of CRP produced by the body varies from person to person, and this difference is affected by an individual's genetic makeup and lifestyle [4].

CRP is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages, which express a receptor for CRP [5].

It is also believed to play another important role in innate immunity, as an early defense system against infections [6].

Several researches have suggests that patients with elevated basal levels of CRP are at an increased risk of diabetes, hypertension, cardiovascular disease and elevated liver enzymes [7-10].

A strong relation was found between highly sensitive CRP and atherosclerosis, which involves the formation of fatty deposits or plaques in the inner walls of the arteries, that is considered in many ways an inflammatory disorder of the blood vessels [11].

Over expression of IL-6 receptor and CRP were observed in HCV-positive patients with hepatocellular carcinoma and liver disease [12].

On the other hand, an increased prevalence of anti-CRP antibodies was manifested in HCV-infected patients suggesting that the presence of anti-CRP antibodies correlated with the presence of RF, cryoglobulinemia, and severity of liver disease [13].

Patients and methods:

The present study was conducted in Baquba General Hospital, Baquba city- Diyala province for the period from 1st. October/ 2005 to 30th. August/2006.

One hundred and five patients with chronic HBV infection and 117 apparently healthy individuals as a control group were enrolled. The both groups were checked for hepatitis B surface antigen HBsAg in their sera by ELISA. The patients include 69 (65.7%) males with mean age 32.4 ± 11.8 years and 36 (34.3%) females with mean age 35.2 ±12.2 years.

The patients were chosen from blood donors and their family contacts plus those referred from the out-patient clinics. The diagnosis of choric HBV infection was based on detection of HBsAg in the patient's sera.

The control group includes 57(48.7%) females with mean age 23.2 ± 5.9 years and 60 (51.3%) males with mean age 28.7 ± 5.9 years. Assessment of CRP titer was done using semi-quantitative tube agglutination test.

All data were statistically analyzed.

Results:

The results showed that 41(35%) of the healthy controls had the lowest CRP titer (zero), while the highest titer 16 was found in 5 (4.3%). The 95% percentile of CRP titer was 8. In chronic HBV carriers, the lowest CRP titer (zero) was found among 4(3.8%), while the highest titer 64 was found in 5(4.7%). The 95% percentile of CRP titer was 32, table (1).

Table (1): Relative frequency of CRP titer among study groups.

CRP titer	Healthy control		Patients with chronic HBV	
	No.	%	No.	%
0	41	35	4	3.8
2	24	20.5	7	6.7
4	19	16.3	13	12.4
8	28	23.9	23	21.9
16	5	4.3	30	28.6
32	0	0	23	21.9
64	0	0	5	4.7
128	0	0	0	0
Total	117	100	105	100
95% percentile	112 (95.7)		100(95.2)	

The range, median, and interquartile range of CRP titer in the study group were shown in table (2). The statistical analyses (Mann-Whitney test) revealed that the median CRP titer in patients was significantly higher as compared to healthy controls (P< 0.001).

Table (2): Range, median, and interquartile range of CRP titer in study groups.

CRP titer	Healthy control	Chronic HBV patients
Range	(0-16)	(0-64)
Median	2	16
Interquartile rane	(0-8)	(8-32)

P (Mann-Whitney) < 0.001

The validity of CRP at a titer 8 as a cut-off value to differentiate between healthy control and patients with chronic HBV infection when the clinical suspicion adjusted at 50%.

The results showed that 33 of healthy individuals had a CRP titer of 8 and more, while 84 of them had a titer less than 8. Among the patient group, 81 had a titer of 8 and more, while 24 of them had a titer of less than 8. The difference between the two groups was statistically significant (P < 0.001), table (3).

Table (3): Validity of CRP titer at 1:8 as a cut-off value.

CRP titer 8 as cut-off value	Healthy control	Chronic HBV patients	Total
Negative (<8)	84	24	108
Positive (≥8)	33	81	219

P < 0.001

Sensitivity = 77%, Specificity = 72%, Positive predictive value = 71%, Negative predictive value = 78%, Accuracy= 74%, False positive = 28%, False negative = 23% (Sorlie DE, 1995) [14]

The validity of CRP at titer 16 as a cut-off value to differentiate between healthy controls and patients with chronic HBV infection when the clinical suspicion adjusted at 50%. The results revealed that only 5 healthy individuals had a titer of 16 and more versus 112 of them had a titer of less than 16. Whereas, in patient group, 58 patients had a titer of 16 and more versus 47 of them had a titer of less than 16. The difference between the two groups was statistically significant (P< 0.001), table (4)

Table (4): Validity of CRP titer at 1:16 as a cut-off value.

CRP titer 16 as cut-off value	Healthy control	Chronic HBV patients	Total
Negative (<16)	112	47	159
Positive (≥16)	5	58	168

P < 0.001

Sensitivity = 55%, Specificity = 96%, Positive predictive value = 92%, Negative predictive value = 70%, Accuracy= 77 %, False positive = 4%, False negative = 45% (Sorlie DE, 1995) [14].

To assess the validity of CRP titer as a predictive marker instead of liver function tests to differentiate between healthy controls of patients with chronic HBV infection, the results showed that the median serum alkaline phosphatase in healthy controls and patients were 56 U/ml and 65 U/ml respectively. The difference between the two values was statistically significant (P< 0.001).

The mean activity of enzyme aspartate aminotransferase in healthy controls and patients was 8 U/ml and 12 U/ml respectively.

The difference between the two groups was statistically significant (P< 0.001). Similarly, the mean activity of alanine transaminase enzyme in healthy control and patients was 10 U/ml and 34 U/ml respectively. The difference between the two groups was statistically significant (P< 0.001).

The mean concentration of serum protein in healthy controls and patients was 5.8 gm/dl and 6.8 gm/dl respectively, with a significant difference between the two groups. Likewise, the mean concentration of total serum bilirubin, direct and indirect bilirubin in healthy controls and patients were 0.6 mg/dl,0.4 mg/dl, 0.2 mg/dl and 1.8 mg/dl, 1.2 mg/dl, 0.5 mg/dl respectively, with significant difference between the two groups (P< 0.001, P< 0.001 and P< 0.001) respectively.

The Spearman's linear correlation between CRP titer and values of liver function tests in healthy control and patients were all significant except the serum alkaline phosphatase and indirect serum bilirubin where there was insignificant correlation, table (5).

Table (5): Spearman's linear correlation between CRP titer and values of liver function tests.

Liver function test	Spearman's linear correlation			
	Healthy control		Chronic HBV patients	
	r	P value	r	P value
S. Alk. Phosphatase	-0.07	0.48 [NS]	0.08	0.42 [NS]
SAST	-0.09	0.34 [NS]	0.21	0.03
SALT	-0.03	0.72 [NS]	0.40	<0.001
Total serum protein	-0.01	0.93 [NS]	0.33	<0.001
Total serum bilirubin	-0.06	0.51 [NS]	0.35	<0.001
Indirect serum bilirubin	-0.06	0.52 [NS]	0.14	0.14 [NS]
Direct serum bilirubin	-0.02	0.83 [NS]	0.33	0.001

r: correlation coefficient

Discussion:

It is well documented that elevated levels of CRP have been found in different infectious and non-infectious medical illnesses as its synthesis is increased in response to infection, inflammation and tissue damage [8-10, 15, 16]. In the present study, the 95% percentile of CRP titer in the sera of patients with chronic HBV infection was 1:32 compared to that in healthy controls 1:8. Therefore, the median CRP titer in patients was significantly higher than that of controls. These results seems not unusual since the target organ for the replication of HBV is the liver leading to destruction of hepatocytes and consequently increase the liberation of CRP which directly proportionate with the degree cellular destruction [17].

Unfortunately, very limited studies have been conducted on the correlation between CRP and viral hepatitis [12,13]. The utility of CRP titer as a predictive marker for the diagnosis of chronic HBV infection in this study showed that the validity of CRP titer 1:16 as a cut-off value is quite sensitive and specific for the diagnosis of chronic HBV infection when the clinical suspension is 50%.

In a previous study, it has been reported that a cut-off value of CRP titer 1:64 can be used for the diagnosis of acute HBV infection when the clinical suspension was 50% by the use of same semi-quantitative tube agglutination test [18].

The results also revealed that there was a significant correlation between the CRP titer and liver function tests, namely aspartate aminotransferase enzyme, alanine transaminase enzyme, total serum protein, and total serum bilirubin, but not alkaline phosphatase enzyme.

These results were consistent with a previous study reported a significant correlation between CRP titer and aspartate aminotransferase, alanine transaminase and gamma glutamyl transferase enzymes in patients with type 2 diabetes mellitus, and attributed the elevation of such enzymes to the increased level of CRP [8]. However, it is inconsistent with another study that found a significant correlation between the CRP and serum alkaline phosphatase enzyme (ALP)[10].

This might be attributed to the fact that the mentioned-study was correlated between ALP and CRP in patients with cardiovascular diseases. The same study mentioned that ALP was significantly higher in patients with diabetes and in those who smoked. Furthermore, high serum activities of ALP have been noted in patients with peripheral arterial diseases [19].

It can be concluded that CRP titer may be a useful marker for the diagnosis of chronic HBV infection when the clinical suspension is 50%.

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