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Major Article

Association of serum levels of C-reactive protein with CRP-717 T/C polymorphism and viremia in HCV and HBV carriers

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Abstract

Introduction: The present study investigated the association of the rs2794521 polymorphism in the *CRP* gene in individuals with chronic hepatitis B and C, correlating it with markers of hepatic inflammation, fibrosis scores, viral load, and plasma protein levels. **Methods:** The study analyzed 185 blood samples obtained from patients with hepatitis B (n=74) and hepatitis C (n=111) and 300 samples from healthy donors. Genotyping was performed by real-time polymerase chain reaction, and protein levels were quantified using the automated immunoturbidimetric method. **Results:** The *TT* genotype was the most frequent in all studied groups and was associated with higher plasma levels of the protein but not with the progression of liver disease. Low levels of C-reactive protein were associated with increased viremia and scores indicative of severe fibrosis and cirrhosis. **Conclusions:** The present results demonstrated a close relationship between the ability of the virus to replicate and cause liver damage and low serum concentrations of C-reactive protein. Future research may determine if these results can be interpreted as a possible form of escape for the virus by decreasing its action as an opsonin and decreasing phagocytosis, which are functions of C-reactive protein in the immune response.

Keywords: C-reactive protein. SNP. HBV. HCV. Viremia.

INTRODUCTION

C-reactive protein (CRP) is synthesized by hepatocytes during acute inflammatory and infectious processes[1], as part of the innate immune response of the host, assisting in the elimination of cell debris from necrosis and apoptosis as well as facilitating phagocytosis through its action as an opsonin[2-4]. In addition, CRP can lead to activation of the classical pathway of the complement system through binding to the C1q protein[2,3].

Serum levels of CRP may increase over a short time period, especially in the presence of an acute stimulus, such as an infection. In the first few hours, this increase may reach 1,000 times the normal value[5]. However, mutations in the *CRP* gene may alter protein function in inflammatory and infectious processes[6-9]. Several single nucleotide polymorphisms (SNPs) in the *CRP* gene were described, and the rs2794521 polymorphism, which is located at position -717 of the promoter region, promotes a T-to-C change and can influence plasma protein levels, once allele T has been correlated with high level of CRP[10].

Although the *CRP*-717 T/C polymorphism is related to the development of acute and chronic inflammatory processes[6,7,11], few studies have evaluated this genetic polymorphism in infectious processes[8,9,12]. In *Hepatitis B virus* (HBV) infection, *CRP*-717 T/C polymorphism evaluation has been restricted to the

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Asian population[8,9]. In contrast, the effect of this polymorphism on *Hepacivirus C* (HCV) infection was not evaluated.

Viral hepatitis is a serious public health problem in several regions of the world. Among the viruses that cause hepatitis, HBV and HCV[13] are the main viruses responsible for the development of chronic liver diseases[14]. The World Health Organization estimates that approximately 325 million people live with chronic HBV or HCV infections worldwide[15].

In HBV, most chronic carriers develop a partial immune response, which is unable to eliminate the virus, resulting in an active infection with persistent inflammatory activity[16]. In HCV infection, approximately 50-80% of individuals are unable to eliminate the virus and develop chronic infection[17], which may progress to liver failure, the main indication for liver transplantation[18].

Considering the important role of CRP in inflammatory processes, which may determine the course of certain diseases, the present study investigated the association of the *CRP*-717 T/C polymorphism in individuals with chronic HBV and HCV in the State of Pará (Brazil), correlating it with markers of inflammation, fibrosis, viral load and plasma protein levels.

METHODS

Study population

A cross-sectional study was performed with 185 consecutive cases of chronic HBV (n=74) and HCV (n=111) patients treated at the hepatology outpatient clinic of Holy House of Mercy of Pará Foundation (Fundação Santa Casa de Misericórdia do Pará) and João de Barros Barreto University Hospital of the Federal University of Pará. The study was conducted from May 2013 to June 2016. Inclusion criteria were as follows: individuals aged 18 years and older; individuals of both sexes; individuals with HBsAg for more than 6 months; and HCV-RNA-positive individuals. Individuals who did not meet the requirements set forth above, patients coinfected with hepatitis virus D (HDV) and/or HIV-1 as well as patients who used or were using antiviral therapy against HBV or HCV were excluded from the study.

All selected patients were clinically evaluated and underwent a complementary screening consisting of hematological, biochemical, serological, virological (viral load), ultrasound, and endoscopic tests as well as liver biopsies (METAVIR scoring). Fibrosis score were defined as: 0 to 2, mild and moderate; and 3 to 4, severe and cirrhosis. The degrees of inflammation were: 0 to 1, mild inflammation; and 2 to 3, severe inflammation. These data were transcribed from the medical records to a form designed specifically for the study.

The healthy control group consisted of 300 blood donors from the Fundação de Hemoterapia e Hematologia do Pará (Center of Hematology and Hemotherapy of Pará) who were negative for serological markers of HBV, HCV, and HDV as well as HIV-1. This group was used to compare the genotype and allele frequencies of the *CRP* -717 T/C polymorphism and plasma protein levels.

The project was submitted to and approved by the Research Ethics Committee of the João de Barros Barreto University Hospital - *Universidade Federal do Pará* (protocol number 962.537) and the Santa Casa de Misericórdia do Pará (protocol number 772.782) in compliance with the guidelines and regulatory requirements for human research. All participants who agreed to participate signed an informed consent form.

Biological samples

Blood samples (5 mL) were collected using a vacuum collection tube containing ethylenediaminetetraacetic acid as an anticoagulant. The samples were then separated into cells and plasma by centrifugation at 5,000 rpm, and stored at -20 °C until time of use.

DNA extraction

Total DNA extraction from peripheral blood cells was performed according to a previously described protocol[19]. The procedure included cell lysis, protein precipitation, DNA precipitation and DNA hydration.

CRP -717 T/C polymorphism (rs2794521) analysis

The presence of the *CRP* -717 T/C polymorphism was investigated in 161 samples from patients with chronic hepatitis, HBV (n=69) and HCV (n=92) by real-time polymerase chain reaction using a StepOne PLUS Sequence Detector (Applied Biosystems, Foster City, CA, USA). Reactions were performed using a predesigned assay (C_318207_20; Life Technologies, Carlsbad, California, USA). Each reaction consisted of 10 µL of TaqMan Universal PCR Master Mix [2X], 1 µL of TaqMan Assay [20X], 6 µL of water and 20 ng of DNA in a final reaction volume of 20 µL. For amplification and detection of alleles, the following program was used: 60 °C for 30 seconds; 95 °C for 10 minutes; and 50 cycles of 92 °C for 30 seconds and 60 °C for 1 minute and 30 seconds.

Plasma quantification of CRP

Plasma levels of CRP were measured by immunoturbidimetry using the CRPeasyDiaSys® kit (DiaSys, Waterbury, CT, USA) on an Architect c8000/Abbott® automated system (Abbott Laboratories Park, Chicago, IL, USA) with a reference < 1 mg/dL.

Statistical analysis

The allele and genotype frequencies were obtained by direct counting. Hardy-Weinberg equilibrium was analyzed on all samples using the Chi-square test (χ^2). The comparative analyses of the allele and genotype frequencies were performed through the G-Test and Chi-square (χ^2) tests. Comparison analyses of enzyme levels (alanine aminotransferase [ALT]; aspartate aminotransferase [AST]; gamma-glutamyltransferase [GGT]) and viral load (HBV and HCV) with CRP levels were performed using the Mann-Whitney Test and the Spearman's Test. Statistical analyses were performed using BioEstat 5.3 software[20] with a significance level of $p < 0.05$. Graphs were generated with GraphPad Prism 5.0 software.

RESULTS

Clinical, biochemical and histopathological data for HBV and HCV carrier populations are described in **Table 1**. The

TABLE 1: Clinical, biochemical and histopathological data in the population with HBV and HCV.

Variables	HBV (n=74)	HCV (n=111)
Liver enzymes		
ALT (IU/L) Mean ± SD (08-54 IU/L)	51.03 ± 51.3	77.64 ± 59.27
AST (UI/L) Mean ± SD (16-40 IU/L)	57.54 ± 79.11	65.35 ± 39.27
GGT (IU/L) Mean ± SD (<50 IU/L)	56.21 ± 90.21	96.87 ± 90.76
Fibrosis scores[a]		
F 0 to 2; n (%)	62 (83.8)	67 (63.3)
F 3 to 4; n (%)	12 (16.2)	34 (33.7)
Inflammatory activity[b]		
A 0 to 1; n (%)	65 (87.8)	54 (58.1)
A 2 to 3; n (%)	09 (12.2)	39 (41.9)

ALT: alanine aminotransferase; **AST:** aspartate aminotransferase; **GGT:** gamma-glutamyltransferase. [a]**Fibrosis score** (0 to 2, mild and moderate; and 3 to 4, severe and cirrhosis) METAVIR; [b]**Degree of inflammation** (0 to 1, mild inflammation; and 2 to 3, severe inflammation). **HBV:** *Hepatitis B virus*; **HCV:** *Hepacivirus C*.

HBV carrier group had a normal mean ALT but elevated levels of AST and GGT. In contrast, the group with HCV infection showed altered levels of all three liver enzymes. In both groups, the majority of patients had mild or moderate fibrosis scores (F0-F2) and absent or mild inflammatory activity levels (A0-A1). Scores indicative of severe fibrosis and cirrhosis (F3-F4) as well as severe inflammatory activity (A2-A3) were found in the group with HCV infection.

CRP -717 T/C polymorphism screening showed that the *T* allele and the *TT* genotype were the most frequent in the studied groups. However, there was no significant statistical difference between the genotype and allele frequencies of HBV and HCV when compared to the control group (**Table 2**). The genotype frequencies of the polymorphism were consistent with Hardy-Weinberg equilibrium in studied groups ($p > 0.05$).

The allele and genotype frequencies did not show significant differences when related to mild (A0-A1) and severe (A2-A3) inflammatory activity levels as well as to mild and moderate fibrosis (F0-F2) and severe fibrosis and cirrhosis (F3-F4) scores (**Table 2**).

With regard to CRP plasma levels, the concentrations of this protein were significantly higher in the group with HBV infection than in the HCV group ($p=0.0213$), and both groups had lower concentrations of the protein than the control group although such differences were only statistically significant ($p = 0.0011$) for the HCV group (**Figure 1A**).

Compared to the control group, the CRP levels were higher in patients with the *TT* genotype, but this difference was not statistically significant (**Figure 1B**). When grouping the patients with viral hepatitis (**Figure 1C**), however, the CRP levels were significantly higher in patients with *TT* genotype than those with *CT* ($p = 0.0012$) and *CC* ($p = 0.0034$) genotypes.

The analysis of the progression of chronic liver disease showed that patients with fibrosis without cirrhosis (F0-F2) had higher levels of CRP ($p = 0.0330$) compared to patients with severe fibrosis and cirrhosis (F3-F4). In contrast, median plasma viral load levels were higher in patients with altered liver parenchyma with METAVIR F3-F4 scores (**Figure 2A and 2D**).

Protein levels were higher in patients with mild or absent inflammation (A0-A1) than in those with moderate and severe inflammation (A2-A3), but these differences were not statistically significant. However, viral load levels were higher in patients with a higher degree of inflammation (**Figure 2B and 2C**).

With regard to liver enzymes (**Figure 3A, B, and C**), plasma CRP levels were significantly higher in patients who had normal

TABLE 2: Distribution of the genotype and allele frequencies of the *CRP*-717 T/C polymorphism in samples from HBV patients, HCV patients, controls and according to the histopathological aspects of the liver.

Genetic profile	HBV n (%)	HCV n (%)	Control n (%)	*p*1	*p*2	Inflammatory activity			Fibrosis score		
						0 to 1 n (%)	2 to 3 n (%)	*p*3	F0 to F2 n (%)	F3 to F4 n (%)	*p*4
Genotypes											
TT	44 (63.8)	53 (57.6)	189 (63.0)	0.9846#	0.2406*	69 (61.6)	27 (58.7)	0.8614#	70 (59.8)	27 (61.4)	0.9797#
CT	23 (33.3)	33 (35.9)	103 (34.3)			38 (33.9)	16 (34.8)		41 (35.1)	15 (34.1)	
CC	02 (02.9)	06 (06.5)	08 (02.7)			05 (04.5)	03 (06.5)		06 (05.1)	02 (04.5)	
Alleles											
***T**	0.80	0.76	0.80	1.0000*	0.6086*	0.79	0.76	0.7349*	0.77	0.78	1.0000*
***C**	0.20	0.24	0.20			0.21	0.24		0.23	0.22	

#G-test, *Chi-square test. ***p*1:** HBV *vs.* control; ***p*2:** HCV *vs.* control. METAVIR; degree of inflammation: ***p*3**: 0 to 1(mild inflammation) vs. 2 to 3 (severe inflammation). Fibrosis score: ***p*4**: 0 to 2 (mild and moderate - Fibrosis) vs. 3 to 4 (severe and cirrhosis - Cirrhosis) **HBV:** *Hepatitis B virus*; **HCV:** *Hepacivirus C.*

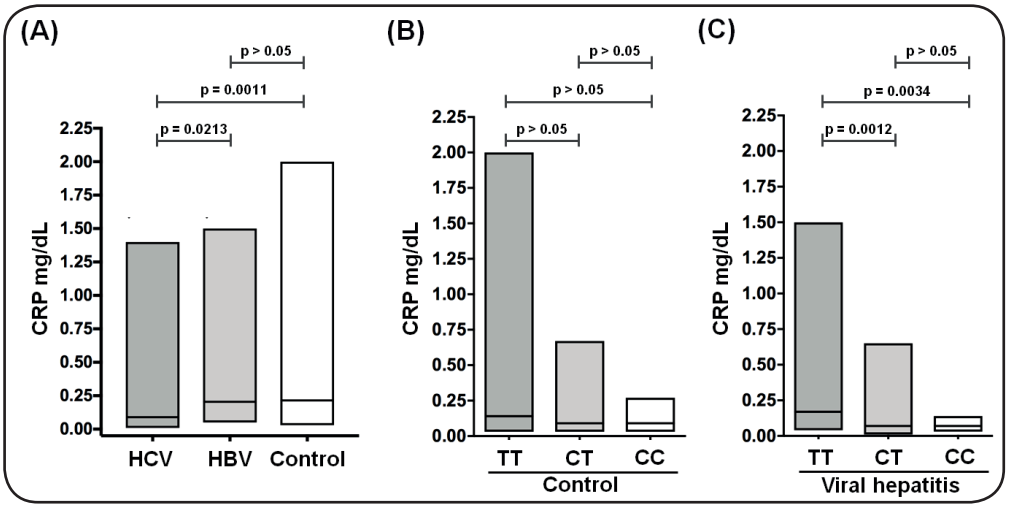

FIGURE1: Serum C-reactive protein concentration. **(A)** Plasma levels of CRP in the groups of patients with chronic hepatitis B, hepatitis C and controls. **(B)** Plasma levels of CRP according to genotypes. **(C)** Plasma levels of CRP according to genotypes in the group of patients with chronic hepatitis B and C. Mann-Whitney test.

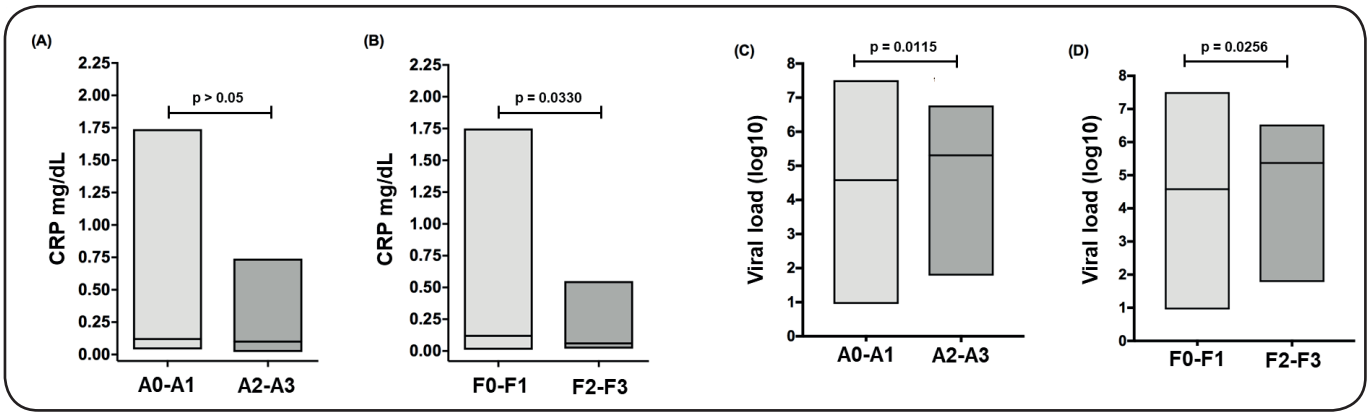

FIGURE 2: Serum C-reactive protein concentration according to infection and clinical conditions of the liver of patients (METAVIR). **(A)** Plasma levels of CRP in patients with fibrosis without cirrhosis (F0-F2) and in patients with severe fibrosis and cirrhosis (F3-F4). **(B)** CRP levels according to mild (A0-A1) and severe liver inflammation (A2-A3). **(C)** Levels of plasma viral load in log10 in patients with fibrosis without cirrhosis (F0-F2) and in patients with cirrhosis (F3-F4). Mann-Whitney test.

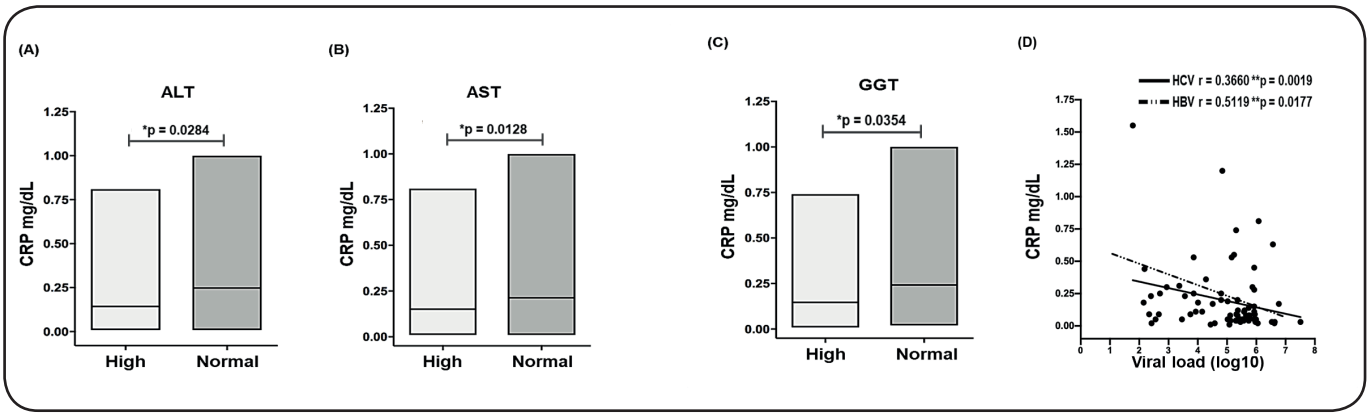

FIGURE 3: Plasma levels of C-reactive protein according to liver enzyme concentrations. **(A)** Elevated and normal ALT. **(B)** Elevated and normal AST. **(C)** Elevated and normal GGT. **(D)** Spearman correlation between plasma C-reactive protein levels and viral load (log10) of HVB (p=0.0177) and HCV (0.0019). *Mann-Whitney test. **Spearman's Test.

levels of ALT, AST, and GGT. **Figure 3D** shows a significant negative correlation between plasma viral load and serum CRP levels in both groups of patients with HBV and HCV.

DISCUSSION

The present study showed that the wild-type *T* allele and the *TT* genotype of the *CRP* -717 T/C polymorphism had the highest frequencies in all the studied groups. The present study also demonstrated that the serum concentrations of CRP were higher in the presence of the *T* allele as compared to the *C* allele, demonstrating that the production levels of the protein are influenced by this genetic variant. These results corroborated findings related to the wild-type *T* allele with a higher transcriptional activity of the *CRP* gene, leading to increased serum protein levels, which may influence an increase in the inflammatory response during early infection[6]. In addition, the relationship between genotypes and the CRP plasma levels was maintained even in the presence of a chronic liver injury caused by HBV and HCV as demonstrated by elevated levels of liver enzymes and changes in liver parenchyma observed in the study population.

CRP is synthesized in the liver by hepatocytes[1] in response to the stimulus produced by interleukin-6 (IL-6) during inflammation and infection[21]. Hepatitis is characterized by destruction of hepatocytes associated with increased release of inflammatory cytokines, which is characterized by increased liver enzymes[22]. The present findings reflected these aspects of the pathophysiology of hepatitis. Lower CRP plasma levels are observed in patients with chronic viral hepatitis with a high degree of persistent hepatic injury (F3-F4) and increased ALT, AST and GGT liver enzymes, whereas higher levels are observed in patients with mild and moderate fibrosis (F0-F2) and those with normal liver enzymes[23-26].

Higher levels of CRP were observed in the serum of patients with HCV prior to treatment with alpha-interferon combined with ribavirin, but the levels decreased after treatment[27]. The present results showed higher plasma concentrations of CRP in the HBV group than in the HCV group. Importantly, 70% of patients with HBV were inactive carriers as characterized by decreased viral replication and, therefore, less liver damage, resulting in maintenance of hepatocyte integrity.

The present results demonstrated a negative correlation between high plasma viral load levels and low CRP levels. Low serum levels of CRP were strongly associated with viremia in HCV patients[23] and elevated levels of IL-6, which is a pro-fibrotic cytokine[24]. However, the stimulatory effect of IL-6 on CRP production in the liver was not observed in patients with active HCV replication, suggesting that virus replication inhibits the effect of IL-6 on CRP. In the present study, reduced levels of CRP in the group of patients with severe fibrosis (F3-F4) were related to greater viral replication because this group presented higher viral load levels.

The present findings corroborated previous studies demonstrating a close relationship between the ability of the virus to replicate and cause liver damage at low CRP concentrations[2,3,28]. However, the present results contrast those reported from a previous study that associated high serum concentrations of CRP with increased HBV replication in patients with chronic infection as reflected by the severity of liver damage[26]. This divergence of results may be related to the methodologies used in data evaluations because unlike the present study[25], the previous study used the receiver operating characteristic curve method for analyses.

The present results demonstrated an association of the *CRP*-717 T/C polymorphism with CRP production levels but not with the progression of chronic infection by HBV and HCV. In contrast, the association found between low serum levels of CRP and increased viremia corroborated the hypothesis of a potential mechanism by which viral replication reduces CRP production[29]. According to this hypothesis, the local immune response of the host becomes altered or refractory to the continued replication of the virus in hepatocytes, resulting in the following complex events that occur during chronic liver disease caused by viral persistence: impairment of cellular components and immune system products in the liver, death of hepatocytes, establishment

of repair fibrosis and low blood flow levels[30]. These factors lead to the decrease of several local immune response mechanisms, such as the decrease of IL-6 production and consequently, the decrease of CRP production during infection[21].

In conclusion, this study showed that HBV and HCV infections are associated with CRP plasma level and chronic liver inflammation. Future research may determine if these findings may be interpreted as a potential escape of the virus from the immune response, and further studies involving other components of the host immune response as well as the effects of using antiviral and antifibrotic therapies that can restore liver function and CRP expression are needed.

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Conflict of interest: The authors declare that there is no conflict of interest.

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