Clinical Medicine Research
2014; 3(2): 44-49
Published online April 10, 2014 (http://www.sciencepublishinggroup.com/j/cmr)
doi: 10.11648/j.cmr.20140302.18

Hepatitis c-virus infection and risk of coronary heart diseases

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To cite this article:
Amin M. Abdel Baki, Nashwa A. Zaky. Hepatitis C-Virus Infection and Risk of Coronary Heart Diseases. *Clinical Medicine Research.* Vol. 3, No. 2, 2014, pp. 44-49. doi: 10.11648/j.cmr.20140302.18

Abstract: Background: The world Health Organization has declared hepatitis C a global health problem, with approximately 3 % of the worlds population. HCV infection was associated with a high risk of CHD. Hs-CRP and fibrinogen was considered as markers of coronary artery disease, their elevation correlated with incidence of CAD, However Apo A deficiency predict future risk of CAD. Aim: To study correlation between HCV infections and marker risk factors of coronary heart disease in different stages of liver disease. Patients & Method: Forty three chronic HCV patients were recruited at specialized hepatology clinic in National Hepatology and Tropical Medicine Research Institute (NHTMRI),Cairo; they were classified into 3 groups according to Child – Pugh score (A, B, C), 42 % were Child class A, 28 % Child B and 30 % Child C, age from 20 to 80 years. 15 healthy subjects served as control group. Detection of the following tests occurred for both groups: Liver function tests: ALT, AST, ALP, total protein, albumin, bilirubin, GGT and AFP. Ultra sensitive CRP, fibrinogen, apoprotein A and Lipid profile: Total Cholesterol, triglyceride, HDL-C, LDL-C, and Total Lipid. Results: the data obtained from results show that :liver enzymes AST, ALT, total bilirubin, albumin, total protein and INR levels were significantly different between groups and control ($p< 0.05$), Alkaline phosphates, GGT and AFP levels were not differing significantly in study groups and control ($p> 0.05$). Cardiac enzymes; CK and LDH levels were not significantly different between groups and control ($p> 0.05$). The APO A levels were not differs significantly in study groups and controls ($p> 0.05$). The fibrinogen andhs-CRP levels in the patients appeared to be significantly higher than those in the healthy controls ($p< 0.05$). Conclusion: hs-CRP and fibrinogen may be considered as a CHC progression prognostic factor, Evidence indicates that hepatitis C virus (HCV) have a key role in coronary heart disease.

Keywords: Fibrinogen, Cardiovascular Disease, Hs-CRP, Hepatitis C Virus, APO A

1. Introduction

The World Health Organization has declared hepatitis C a global health problem, with approximately 3% of the world's population (roughly 170-200 million people) infected with HCV. There are about 35,000 to 185,000 new cases a year in the United States. In Egypt the situation is quite worse; the national prevalence rate of HCV antibody positively has been estimated to be 10-13 %(1), up to 20% in some areas nearly seven out of every 1,000 Egyptians acquire HCV infections every year (2)

After exposure, the majority of HCV-infected patients develop chronic infection, manifested by the persistence of HCV RNA in the blood. HCV exerts its main effects on the liver, inducing inflammation that leads to progressive hepatic fibrosis and ultimately cirrhosis in approximately 20% of those chronically infected (3). Liver cirrhosis is the final common histological pathway for a wide variety of liver diseases. Several scoring systems have been proposed for grading and staging chronic viral hepatitis as Child-Pugh score which has been extensively used to describe severity and prognosis of the disease (4, 5).

Chronic HCV infection has been associated with numerous extrahepatic manifestations; these manifestations can involve multiple organ system, including renal, dermatologic, hematologic and rheumatologic systems (6, 7). However, its impact on cardiovascular disease remains unclear (8).

The association between hepatitis C virus (HCV) infection and coronary artery disease (CAD) is controversial. Some studies have reported no association between HCV infection and CAD, whereas others have reported an increased risk. Very recent data have indicated that HCV infection was associated with a higher risk of CHD, after

the adjustment of traditional risk factors (9), and seropositivity for HCV may have a role in the pathogenesis of carotid atherosclerosis (3). Furthermore; HCV infection may independently predict an increased severity of CHD (9). The aim of this work was to study correlation between HCV infections and marker risk factors of coronary heart disease in different stages of liver disease.

2. Patients and Methods

The study was revised and approved ethically by the institutional review board (IRB). Fifty eight persons were enrolled from specialized hepatology clinic in National Hepatology and Tropical Medicine Research Institute (NHTMRI),Cairo, Egypt during the period from september 2011 to January 2012: the patients (n=43) had chronic HCV infection chosen on the basis of HCV- Abs, and Positive HCV-RNA. , Both HCV antibodies and RNA were detected in the serum of all studied patients. Anti-HCV antibody was measured by the third generation Abbott HCV EIA 3.0 (Abbott Laboratories, Ludwigshafen, Germany). HCV RNA was detected by RT-PCR QIAmp Viral RNA Kit (QLAGEN, Santa Clarita, USA). Patients with liver disease classified according to Child-Pugh Score class A to C, Score A includes 18 patients, 16 males and 2 females with average age 39.72 ± 10.35 years, Score B includes 12 patients, 8 males and 4 females with average age 46 ± 9.99 years, Score C includes 13 patients, 12 males and one female with average age 53.77 ± 11.39 years. A group of healthy control (n=15) matched with patients group as regard age &sex.

After getting an informed consent, all patients &control persons were subjected to the following:

Full medical history taking, complete physical examination & laboratory investigation including: CBC, Liver function tests(ALT, AST, ALP, GGT activities ,serum bilirubin, prothrombine time and INR, albumin , total protein and Alfa feto protein (AFP) levels, , cardiac function enzymes(serum lactate dehydrogenase (LDH) and creatine kinase (CK) activities, lipid profile (total cholesterol, triglycerides, HDL-C and LDL-C levels), serum hs-CR-protein level, detection of plasma fibrinogen, apoprotein A level, and abdominal ultrasound

Inclusion criteria: presence of HCV-Ab by (ELISA), positive HCV-RNA by PCR.

Exclusion criteria: other liver diseases not related to HCV e.g. HBV, autoimmune hepatitis and other diseases; such as diabetes, hypertension, renal diseases.

4.3. Statistical Analysis

The statistical analysis of the data carried out by the aid of excel data sheet .The data obtained in the present study were expressed as mean ±SD. All statistical analyses were performed using the Statistical Program for Sial Sciences (SPSS) statistical software (Version 17.0, Chicago, IL, USA). p= probability value. ($p>0.05$ = not significant, $P<0.05$ = significant, $p =0.001$ = highly significant).

Independent samples't' test was used to compare numeric variables between the two groups. Pearson's correlation coefficient (r) values were calculated to check the linear correlations between lipid profile and inflammatory markers.

Table 1. *Serum total cholesterol, triglycerides, HDL-C and LDL-C in patients with HCV.*

	Child Pugh A	Child Pugh B	Child Pugh C	Control	P value
Total Cholesterol mg/dl	163.2 ± 49.73	161.8±49.88	182.1±53.54	185.1± 25.36	0.381
Triglycerides mg/dl	95.39±42.96	105.9±39.11	125.5±43.08	87.67±19.83	0.057
HDL mg/dl	37.83±8.84	38.17±11.69	33.77±8.32	41.8±5.49	0.128
LDL mg/dl	106.3±45.84	102.4±47.9	123.2±48.13	125.8±25.6	0.362

r= Pearson's correlation coefficient; A correlation is a number between -1 and +1 that measures the degree of assiation between two variables (call them X and Y). A positive value for the correlation implies a positive assiation (large values of X tend to be assiated with large values of Y and small values of X tend to be assiated with small values of Y). A negative value for the correlation implies a negative or inverse assiation (large values of X tend to be assiated with small values of Y and vice versa). Perfect: If the value is near ± 1, then it said to be a perfect correlation. High degree: If the value lies between ± 0.75 and ± 1, then it is said to be a high degree of correlation.

Moderate degree: If the value lies between ± 0.25 and ± 0.75, then it is said to be moderate degree of correlation. Low degree: When the value lies between 0 and ± 0.25, then it is said to be a low degree of correlation. No correlation: When the value is zero.

3. Results

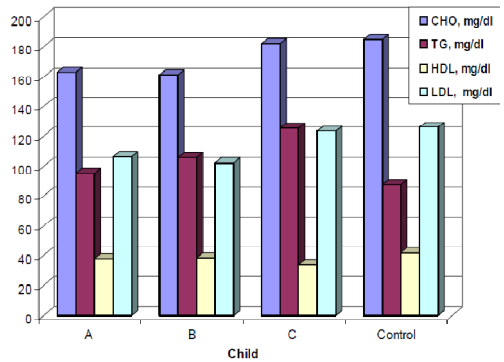

Figure 1. *Serum total cholesterol, triglycerides, HDL-C and LDL-C in patients with HCV.*

Table (2) and figure (1) show that the serum total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride concentrations levels were not differ significantly between the patient groups and healthy control (p> 0.05). Triglyceride was increased in groups when compared to healthy control subject.

Table 2. *Serum fibrinogen, hs-CRP and APO A levels in patients with HCV.*

		N	Mean ±SD	P value
FIB mg/dl	A	18	287±79.49	0.004
	B	12	297.5±89.65	
	C	13	316±87.01	
	Control	15	211.93±53.19	
HsCRP µg/ml	A	18	1.34±1.34	0.009
	B	12	3.67±5.04	
	C	13	4.5±4.79	
	Control	15	0.71±0.53	
APOA g/L	A	18	2.23±1.08	0.305
	B	12	2.08±1.11	
	C	13	2.33±1.09	
	Control	15	1.67±0.73	

Table (3) show that The APO A levels were not differs significantly in study groups and controls (p> 0.05). The fibrinogen and hs-CRP levels in the patient groups appeared to be significantly higher than those in the healthy control subject (p< 0.05).

Table 3. *the prevalence of hs-CRP in Child-pugh score A, B and C.*

HsCRP normal range	*A*	*B*	*C*
< 1 µg/dl	*61 %*	*33%*	*30%*
1-3 µg/dl	*27%*	*25%*	*23%*
>3 µg/dl	*11%*	*33%*	*46%*

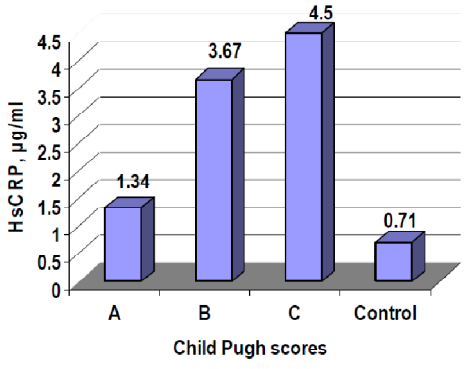

Figure 2. *Serum hs-CRP levels in patients with HCV.*

Table(4) and figure(2) show that the mean value for hs-CRP level was significantly higher in patient groups than in healthy control and tended to be higher in group C(4.5 ±4.78) than group A and B(1.34 ±1.34,3.67 ±5.03)µg/ml respectively.

Table 4. *Correlation coefficients between lipids and hs-CRP, fibrinogen and apoprotein A.*

Variables		*TC*	*TG*	*HDL*	*LDL*
HsCRP	*r*	*0.108*	*0.350*	*-0.271*	*0.109*
	p	*0.418*	*0.007*	*0.040*	*0.415*
FIB	*r*	*-0.084*	*0.385*	*-0.187*	*-0.122*
	p	*0.529*	*0.003*	*0.160*	*0.361*
APOA	*r*	*-0.092*	*-0.021*	*-0.031*	*-0.089*
	p	*0.491*	*0.878*	*0.817*	*0.507*

p= probability value. (p>0.05 = not significant, P<0.05 = significant, p =0.001 = highly significant). r= Pearson's correlation coefficient.

Table (5) shows that a significantly positive correlation was found between hc-CRP and triglyceride(r=0.350) this show moderate degree of association i.e. hc-CRP directly proportional with TG, a significantly negative correlation was found between hc-CRP and HDL cholesterol(r= -0.271) i.e. inversely proportional, but insignificant correlation was found between hc-CRP and total cholesterol(r= o.o108), and LDL cholesterol(r= o.o109) in hepatic patients i.e. there was no linear relation.

Pearson's correlation coefficient values between FIB and triglycerides(r= 0.385) was significantly positive but insignificant correlation was found between FIB and total cholesterol(r= -0.084), HDL cholesterol(r= -0.187) and LDL cholesterol(r= -0.122) in hepatic patients. Insignificant correlation was found between APO A and lipids) in hepatic patients.

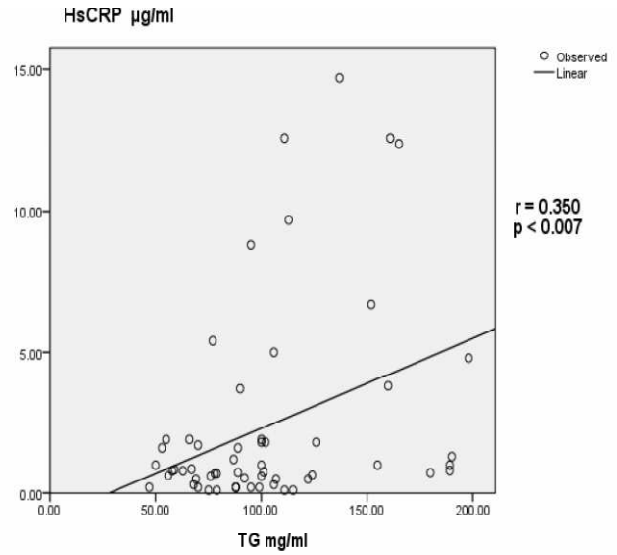

Figure 3. *represent the correlation between hs-CRP and triglycerides in all hepatic patients.*

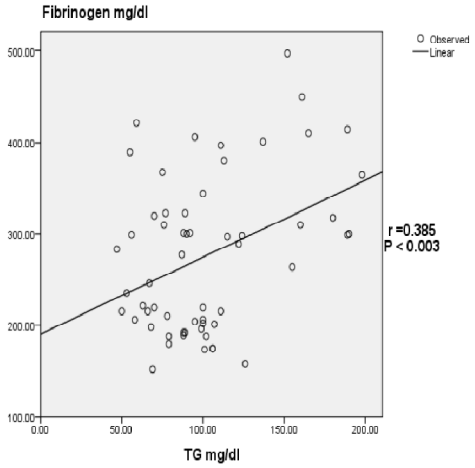

Figure 4. *represent the correlation between fibrinogen and triglycerides in all hepatic patients.*

Table 5. *Relationship between HCV RNA level and hc-CRP,fibrinogen and apoprotein A.*

		N	Mean ±SD	P value
FIB mg/dl	C	15	211.93±53.19	0.001
	L	13	269.92±68.80	
	M	29	307.38±86.27	
	H	1	421	
HsCRP µg/ml	C	15	0.71±0.53	0185
	L	13	3.29±4.83	
	M	29	2.86±3.70	
	H	1	0.84	
APOA g/L	C	15	1.67±0.73	0.060
	L	13	1.83±0.98	
	M	29	2.35±1.08	
	H	1	3.50	

4. Discussion

HCV is a major etiologic agent of chronic hepatitis (10, 11). About 170 million individuals can be found with chronic hepatitis C viral infection all over the world**.** The World Health Organization (WHO) estimates a worldwide prevalence of 3%. In Middle Europe, approximately 1% of the population is infected, mostly with genotype 1 (85% in Austria), at least 21.3 million HCV carriers in the Eastern Mediterranean countries (12)**.**

In Egypt, hepatitis C is a major public health problem and competes with Schistosomiasis as leading causes of chronic liver disease. Most of chronic liver disease was due to chronic infection with hepatitis C virus. The HCV genotype 4 affects approximately more than 90% of Egyptian patients with Hepatitis C (13, 14).

Coronary artery disease (CAD) is one of the commonest causes of mortality and morbidity all over the world. Risk factors for CAD include; conventional factors like hypertension, diabetes mellitus, smoking, hyperlipidemia and central obesity at a younger age, and new risk factors include hs-CRP and fibrinogen (15).

The association between hepatitis C virus (HCV) infection and CAD is less clear. A small number of reported studies have shown conflicting results; some have reported no association between HCV infection and CAD (16) whereas others have reported an increased risk (3).

Some evidence revealed that HCV infection is associated with a higher risk of CAD, even after adjustment for traditional risk factors (9).There is also a variety of evidence for a role for HCV in the atherosclerotic process(17,18). Matsumori et al., revealed that in addition to atherosclerosis, HCV may be involved in cardiovascular diseases such as myocarditis and cardiomyopathies(19). HCV sero–positivity might be considered one of the risk factors for coronary artery disease, independent of other conventional determinants for atherosclerosis. Identification of viral genomes in the atherosclerotic plaques and pro-atherogenic effects of viral infection in cells was relevant to atherogenesis (3).

The main purpose of this study was investigating the relationship between chronic hepatitis C infections in different stages of liver cirrhosis according to Child – Pugh score classification which classify hepatic patients into three groups A, B and C and HsCRP, fibrinogen and Apoprotein A as marker risk factors of coronary heart disease.

In the current study, the serum total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides levels did not differ significantly between the hepatic patient groups and healthy control subjects. Our results disagree with Siagris et al., Dai et al., Judith et al ,Butt et al., and Lao et al., who found that low levels of serum lipids were reported in subjects chronically infected with the hepatitis C virus. Postulated mechanisms for lower lipid levels in HCV-infected persons include binding of HCV particles to various lipid fractions, impaired hepatocyte assembly of very-low-density lipoprotein because of inhibition of microsomal transfer protein, and entry of HCV into hepatocytes through the LDL-C receptors. HCV viremia is associated with clinically significant lower cholesterol levels (TC, LDL, and HDL) when compared with those of normal subjects (20, 21, 22, 9, 23).

C-reactive protein (CRP) is a biomarker for inflammation and is associated with increased coronary artery disease and cardiovascular events. In the most recent comprehensive meta-analysis, high-sensitivity C-reactive protein (hs-CRP) was consistently found to be an independent predictor of CVD (24).

In the present study, we revealed that, the mean value for hs-CRP level was significantly higher in hepatic patient groups than in healthy control subjects and tended to be higher in group C than groups A and B. The results obtained agree with Memon et al., Huang et al., and Lidija et al.,(25,26,27), but disagree with Nascimento et al. and Judith et al.,(28,22). Huang et al., found that Chronic HCV infection (CHC) patients had a higher hs CRP level than healthy controls (25). Lidija et al., suggested that hsCRP, as

an inflammatory marker, is also increased in CHC, being an inflammatory liver disease (27). Hashimoto et al.,demonstrated that the high sensitivity (hs) CRP concentration was independent predictor of the development of early carotid atherosclerosis. They showed that hs-CRP was a marker oh inflammation related to the rate of plaque development rather than of the extent or severity of the plaque burden. Similarly, also there was no association between CRP and the severity of carotid atherosclerosis in a study of hs-CRP (29).

Karantza et al., reported that correlations between level of hs-CRP with LDL-C and HDL-C were weak and non-significant; and correlation with HDL-C was negative. Otherwise, hs-CRP was significantly associated with triglycerides (30).

In our results, significantly positive correlation was found between hs-CRP and triglyceride (r=0.350) this show moderate degree of association i.e. hs-CRP directly proportional with triglycerides, A significantly negative correlation was found between hs-CRP and HDL cholesterol (r= -0.271), i.e. inversely proportional, but insignificant correlation was found between hs-CRP and total cholesterol (r=0.108), and LDL cholesterol (r=0.109) in hepatic patients, i.e. there was no linear relation.

Sabeti et al., and Nikolaos et al., reported that fibrinogen levels were significantly higher in patients presenting with fatal or non-fatal coronary heart disease, in advanced atherosclerotic plaques fibrin participates in the close linkage of low density lipoprotein (LDL) and lipid accumulation, leading to the creation of the lipid nucleus of atherosclerotic lesions. Fibrinogen and its metabolites may lead to endothelial dysfunction (31, 32). Gil et al., proved that plasma fibrinogen level may be an important diagnostic tool in assessment of patients with chest pain (33). Alyan et al., reported that fibrinogen level was significantly higher in the HCV seropositive group (34). Saatea et al., found that plasma fibrinogen level of the patients was highly variable in different stages of cirrhosis, and are an important non invasive prognostic tool which may be helpful in the management of patients, before they develop the complications of the disease (35). Our data showed that the mean value for plasma fibrinogen was significantly higher in hepatic patients than in healthy control subjects and tended to be higher in group C (316 ± 87.01) than group A and B (287 ± 79.49, 297.5 ± 89.65) mg/dl respectively. The higher fibrinogen and CRP levels in the HCV seropositive group suggest greater severity of atherosclerosis. Fibrinogen, an acute-phase protein, is strongly associated with atherosclerosis and also with a number of cardiovascular risk factors.

In the present study, no significant relationship found between HCV-RNA quantitative level and APO A or HsCRP levels, in other way the APO A and hs-CRP levels did not differ significantly in patient groups and healthy control subjects. However, there was a statistically significant relationship between the serum quantitative HCV-RNA titers and fibrinogen levels. The fibrinogen levels in patient groups appeared to be significantly higher than those in the healthy control subjects.

Hepatitis C virus (HCV) RNA is the most important indicator of viral replication in patients with Hepatitis C. HCV- RNA, which is a significant parameter in terms of detection of viremia in serum, the trend of the infection, and particularly the response to treatment, can be quantitively detected with polymerase chain reaction (PCR) (36).

Radkowski et al., and Boddi et al., found that HCV RNA replicate in plaque tissue suggested that an active local infection. This in turn makes it conceivable that the virus may exert local action in carotid atherosclerosis (37, 38). Vassalle et al., proposed that identification of viral genomes in the atherosclerotic plaques and pro-atherogenic effects of viral infection in cells was relevant to atherogenesis (3).

Conclusion: Hs-CRP and fibrinogen levels rise with chronic HCV and cirrhosis progression. The higher hs-CRP and fibrinogen levels in HCV seropositive group, suggest greater severity of CHD. Fibrinogen has a significant relationship with HCV viremia, but hs-CRP and Apoprotein A have no significant relationship with HCV viremia. Therefore they are a useful prognostic parameter. We concluded that; HCV seropositivity might be considered one of the risk factors for CHD.

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