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The Association Between Systemic Hypertension and Chronic HCV-4 Infection

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Abstract: Patients with chronic hepatitis C virus infection are more likely to have systemic hypertension, in addition to insulin resistance and diabetes. The present study aimed to evaluate the association between systemic hypertension and chronic HCV-4 infection among Egyptian patients. This cross-sectional study evaluated the existence of systemic hypertension among one thousand adult Egyptian subjects (500 patients with chronic HCV-4 infection versus 500 non infected subjects who served as a control group). Prevalence of systemic hypertension was significantly higher among patients with chronic HCV-4 infection (38.8%) than among the controls (21.8%) (P=0.001). 30.3% of all hypertensive patients were not aware of their illness; the rate of non-awareness among hypertensive patients with chronic HCV-4 infection was 22.68% while that of non infected subjects was 44.04% ($p < 0.05$). A statistically significant higher rate of systemic hypertension was found among diabetic patients. In conclusion, significant association exists between chronic HCV-4 infection and systemic hypertension especially among diabetic patients. Patients with chronic HCV infection are more aware of their systemic hypertension than non infected subjects.

Keywords: Hypertension, Hepatitis C-4, Diabetes

1. Introduction

Chronic HCV infection is recognized as a systemic disease involving lipid metabolism, oxidative stress, and mitochondrial function [1]. Chronic hepatitis C infection has many aspects which suggest that this disease must be viewed not only as a viral disease but also as a metabolic disorder which implies: insulin resistance (IR) [2], hepatic steatosis [3], impaired glucose tolerance [4], type 2 diabetes mellitus (DM) [5], and altered lipid metabolism [6].

The consequences of IR and DM in HCV-infection can be divided into those that affect liver outcomes and those affecting non hepatic- related outcomes [7]. HCV patients with DM or IR tend to have higher stages of hepatic fibrosis and lower efficacy of antiviral treatment [8]. In addition to metabolic disturbances, HCV has also been associated with atherosclerosis and coronary artery disease [9–11]. Although HCV and its contribution to DM and IR can explain some of these associations, the exact underlying mechanism of how chronic HCV infection can predispose to cardiovascular complications remains unclear [12]. Viral factors such as HCV genotypes and HCV core protein can have a direct impact on these complications [9].

Despite the large pool of researches that have documented a relationship between chronic HCV infection and various cardiovascular disorders [13-15], insufficient number of clinical trials was conducted to directly assess the prevalence of systemic hypertension among chronic HCV infected patients. To the best of our knowledge Younossi Z. M. 2013 [12] was the first to report a direct, independent association between chronic HCV infection and systemic hypertension. The present study aimed to evaluate the association between systemic hypertension and chronic HCV-4 infection among Egyptian patients.

2. Subjects and Methods

This study was a randomized, cross-sectional comparative study that was conducted in the cardiology and hepatology clinics of Ain Shams University Hospitals, Cairo, Egypt. The study was performed according to the ethical standards for human experimentation approved by the human research committee of Ain Shams University Hospitals. Informed consents were obtained from all participants.

1000 adult Egyptian subjects were recruited and divided into 2 groups as follows: group I included 500 patients with chronic HCV-4 infection, all these patients were candidate for HCV treatment and all had a positive Polymerase Chain Reaction (PCR) test for HCV RNA. Group II included 500 non infected subjects who served as a control group. 49 patients of group I and 29 subjects of group II had history of type 2 DM for which they received oral treatment (Sulphonylureas ± Biguanides).

All subjects were subjected to the following:

a) History taking, clinical examination, calculation of Body Mass Index (BMI), Abdominal ultrasonography scan, laboratory investigations including: fasting and 2h post prandial blood glucose level, lipid profile, liver function tests, Alpha-fetoprotein, prothrombin time & INR, renal function tests, complete blood count (CBC), ESR, Rheumatoid factor, urine analysis, iron study, glycosylated hemoglobin (HbA1c), free T3, free T4, TSH, ANA, HBs Ag, HIV and HCV antibodies using 3rd generation ELISA technique.

b) HCV genotyping was based on epidemiologic assumption [16].

c) Oral Glucose Tolerance Test (OGTT) was done for subjects who had no history of DM. The test was performed as described by the World Health Organization (WHO) using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. Criteria for the diagnosis of DM: Fasting Plasma Glucose (FPG) > 126 mg/dl or 2-h plasma glucose > 200 mg/dl. Impaired Fasting Glucose: FPG 100–125 mg/dl, Impaired Glucose Tolerance: 2-h plasma glucose 140– 199 mg/dl [17].

d) Blood Pressure Measurement**:** Participants were initially evaluated during a 1-hour visit. Most of the visit was devoted to administration of an interview focused on health conditions and associated risk factors. The interview included four questions related to the diagnosis and treatment of high blood pressure (Figure 1) [18]. At the end of the interview, the participant's blood pressure was measured three times. A second set of blood pressure measurements was obtained during physical examination. In both settings, blood pressure was measured with the participant in the sitting position after 5 minutes of rest. A standard mercury sphygmomanometer was used, and one of four cuff sizes [pediatric, regular adult, large, or thigh] was chosen on the basis of the circumference of the participant's arm, as indicated by the manufacturer's guidelines. Three blood pressure measurements were obtained, with at least 60-second interval between each measurement [19].

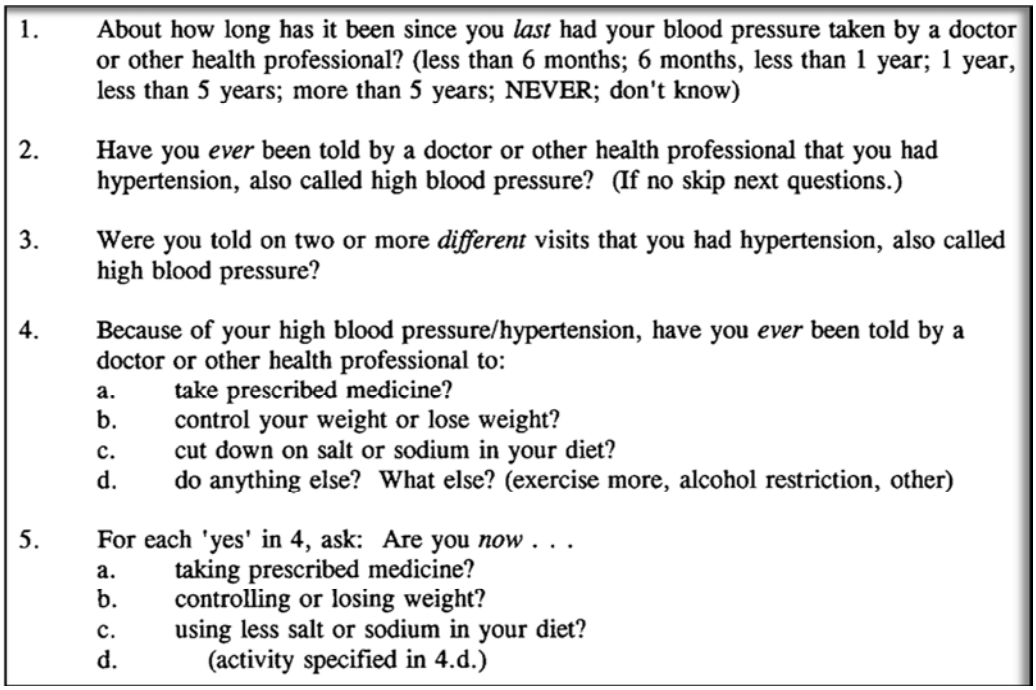
Hypertension was defined as mean systolic blood pressure [SBP] ≥140 mm Hg, mean diastolic blood pressure [DBP] ≥90 mm Hg, or current treatment for hypertension with prescription medications [20]. Treatment of hypertension was defined as use of a prescription medication for management of high blood pressure at the time of the interview. Awareness of hypertension reflects any prior diagnosis of hypertension or high blood pressure by a health professional. Control of hypertension was defined as treatment of hypertension associated with SBP <140 mm Hg and DBP <90 mm Hg [21].

Subjects were excluded from the study if they had any of the following conditions: decompensated liver cirrhosis, evidence of secondary hypertension, any autoimmune disorder, acute or chronic kidney disease, organ transplant recipient, current or past history of any malignancy, any thyroid disorder, current or past history of heavy alcohol consumption or intravenous drug abuse, HIV infection, patient who received any form of immunosuppressive or antiviral therapy, patients receiving any treatment known to affect the blood pressure (i. e.: Glucocorticoids, mineralocorticoids, prolonged use of NSAIDs, nasal decongestants), pregnant and/or nursing females, patients with other liver diseases as alcoholic liver disease, non alcoholic fatty liver disease, drug-induced hepatitis, other viral hepatitis, hereditary haemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and alpha-1 antitrypsin deficiency**.**

Data analysis and Statistical methods: data were collected, coded and entered to a personal computer IBM compatible 2.6 GHz. Data were analyzed with the program statistical package for social science (SPSS). The following tests were used: calculation of the mean values and standard deviations, Student t-test (t), Chi-square test (χ^2). The probability value (P) was expressed as following: $P > 0.05$: non-significant, $P \leq 0.05$: significant, $P < 0.01$: highly significant.

3. Results

One thousand Egyptian subjects were recruited from the outpatient clinic and were classified into 2 groups as follows: group I included 500 patients with chronic HCV-4 infection. Group II included 500 non infected subjects. 49 patients of group I and 29 subjects of group II had type 2 DM of ≥ 1 year duration for which they received Sulphonylureas ± Biguanides. Group I included 282 males and 218 females, their age ranged from 18 to 70 year (mean age 45.188 ±15.11 year). The control group included 230 males and 270 females and their age ranged from 20 to 74 year (Mean age 46.087±18.77 year) ($p > 0.05$).



1. About how long has it been since you *last* had your blood pressure taken by a doctor or other health professional? (less than 6 months; 6 months, less than 1 year; 1 year, less than 5 years; more than 5 years; NEVER; don't know)

2. Have you *ever* been told by a doctor or other health professional that you had hypertension, also called high blood pressure? (If no skip next questions.)

3. Were you told on two or more *different* visits that you had hypertension, also called high blood pressure?

4. Because of your high blood pressure/hypertension, have you *ever* been told by a doctor or other health professional to:
   a. take prescribed medicine?
   b. control your weight or lose weight?
   c. cut down on salt or sodium in your diet?
   d. do anything else? What else? (exercise more, alcohol restriction, other)

5. For each 'yes' in 4, ask: Are you *now* . . .
   a. taking prescribed medicine?
   b. controlling or losing weight?
   c. using less salt or sodium in your diet?
   d. (activity specified in 4.d.)

Figure 1. *Third National Health and Nutrition Examination Survey (NHANES III) questionnaire items on hypertension. Source: NHANES III, the centers for disease control and prevention, and the national center for health statistics.*

History taking and clinical examination revealed that 194 patients with HCV-4 infection (38.8%) had systemic hypertension, while the prevalence of hypertension among the control group was 21.8% (109/500) ($p < 0.05$) (table 1).

Table 1. *Comparison between studied groups as regards HTN.*

HTN	Group I		Group II		Total	
	number	%	number	%	number	%
Non hypertensive patients	306	61.20	391	78.20	697	69.70
Hypertensive patients	194	38.80	109	21.80	303	30.30
Total	500	100	500	100	1000	100

Chi-square=33.411, P-value<0.001

30.3% of hypertensive patients of both groups were not aware of their illness. The rate of non-awareness among hypertensive patients of group I was 22.68% while that of group II was 44.04% ($p < 0.05$).

9.8% of HCV -4 infected patients and 5.8% of non infected subjects had history of type 2 DM ($p < 0.05$). A statistically significant higher rate of systemic hypertension was found among patients with chronic HCV infection who had type 2 DM (table 2, 3).

Table 2. *Comparison between studied groups as regards DM.*

DM	Group I		Group II		Total	
	number	%	number	%	number	%
Non diabetic patients	451	90.20	471	94.20	922	92.20
Diabetic patients	49	9.80	29	5.80	78	7.80
Total	500	100	500	100	1000	100

Chi-square=5.020**,** P-value 0.0025

Table 3. *DM and HTN in group I.*

HTN	Non diabetic patients		Diabetic patients		Total	
	number	%	number	%	number	%
Non hypertensive patients	283	62.75	23	46.94	306	61.20
Hypertensive patients	168	37.25	26	53.06	194	38.80
Total	451	100.00	49	100.00	500	100.00

Chi-square=4.011**,** P-value 0.045

Comparison between both groups regarding risk factors for developing HTN (smoking, obesity and positive family history) showed insignificant differences ($p > 0.05$) (figure 2, 3&4).

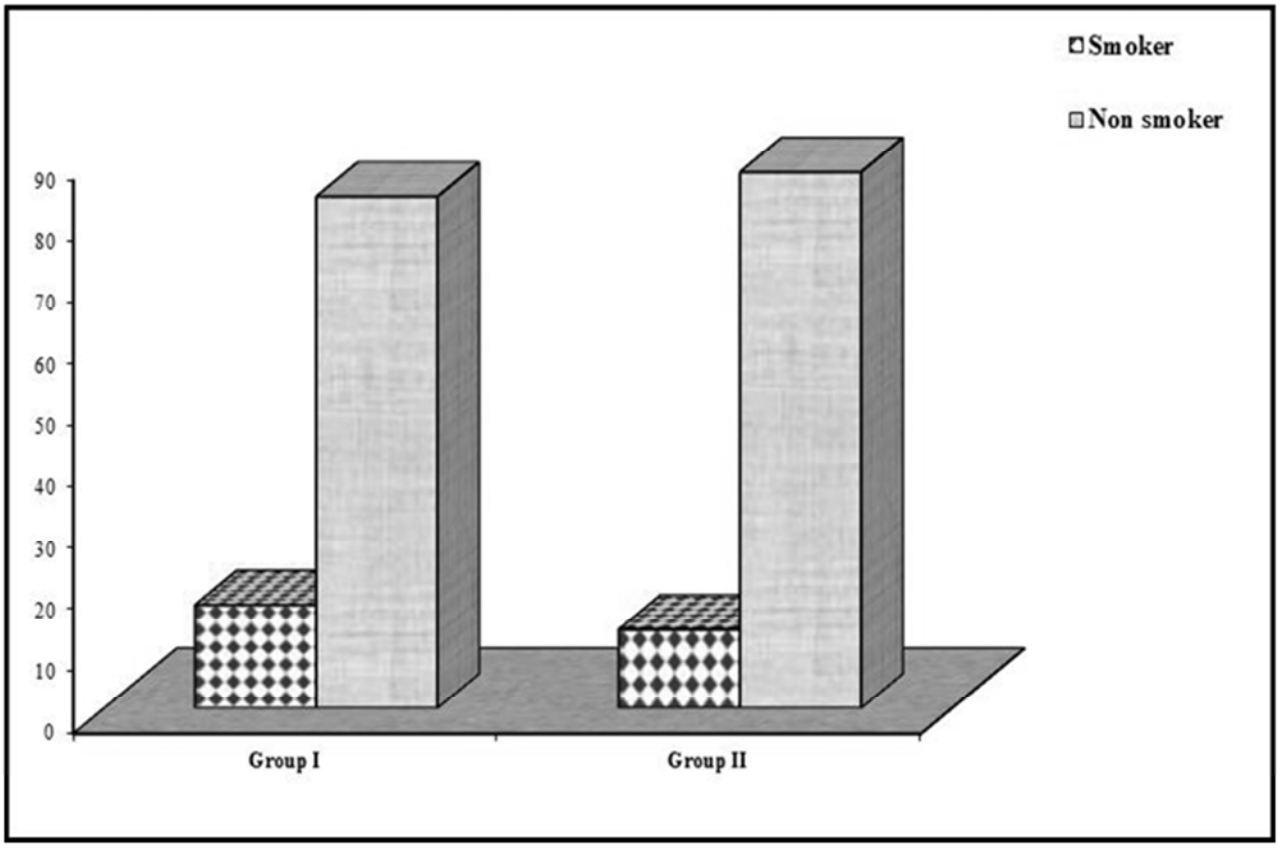


Figure 2. *Comparison between studied groups as regards smoking.*

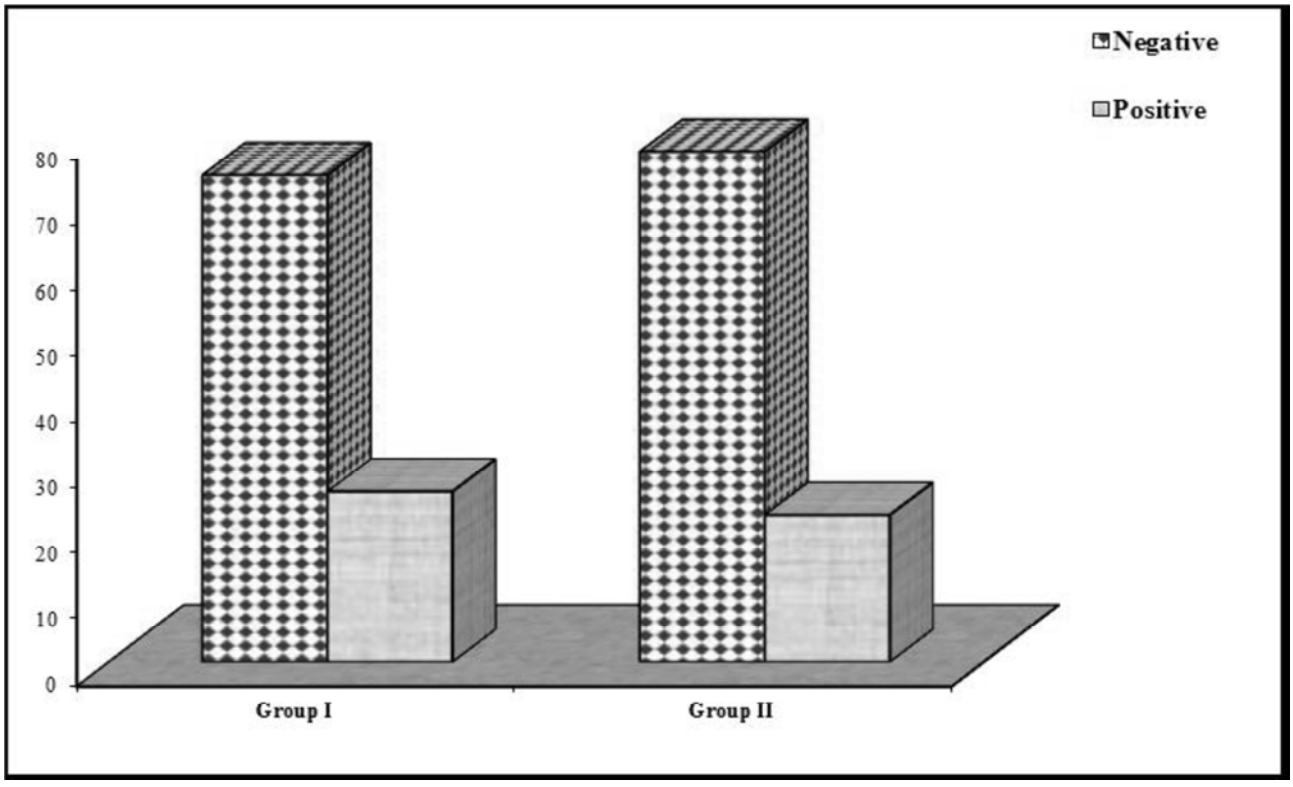


Figure 3. *Comparison between studied groups as regards obesity.*

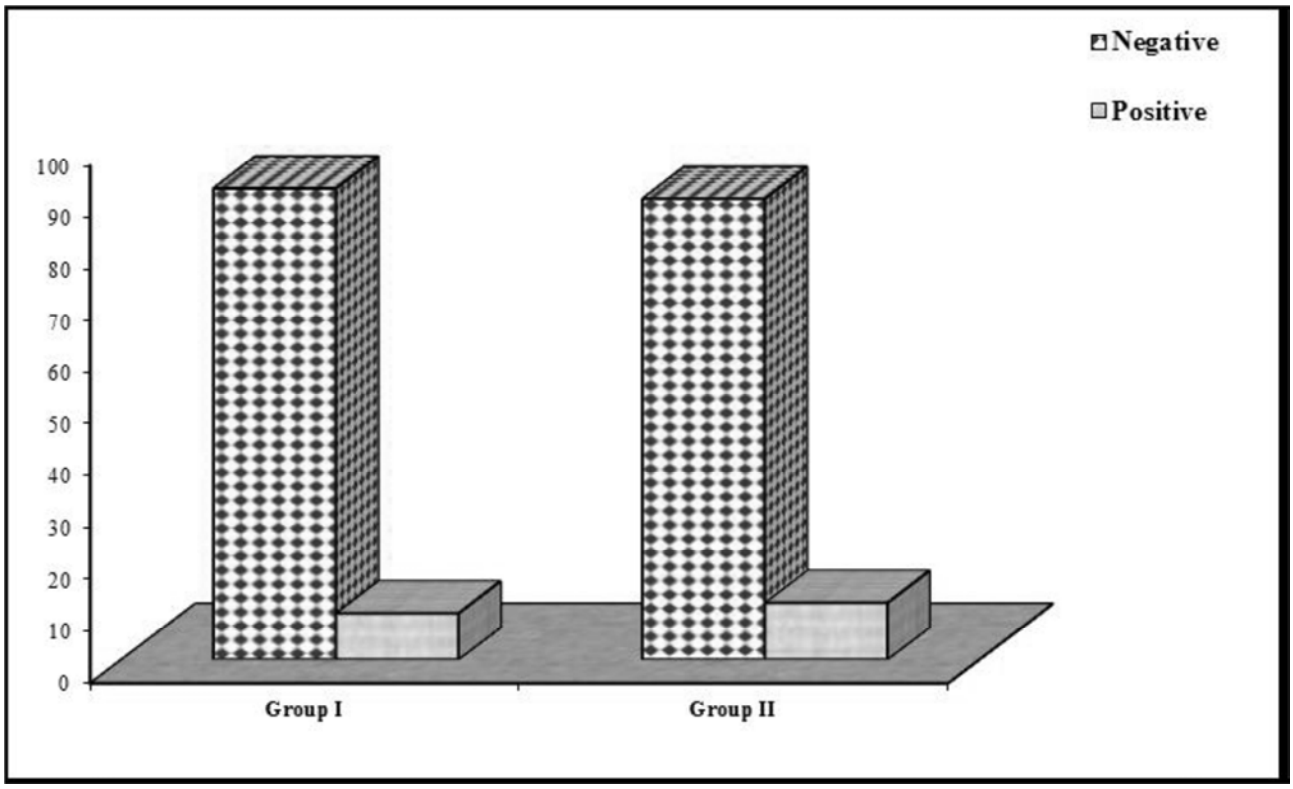


Figure 4. *Comparison between studied groups as regards family history of hypertension.*

In group I, the differences between hypertensive and non hypertensive patients regarding liver function tests (ALT, direct bilirubin and serum albumin) were insignificant ($p > 0.05$) (table 4).

Table 4. *HTN and liver function tests in group I.*

	HTN		T-test	
	Hypertensive patients (n=194)	**Non hypertensive patients (n=306)**	**t**	**P-value**
ALT (20-65U/L)	52.54±30.154	52.51±24.144	0.012	0.9902
Direct bilirubin (0.1-0.4 mg/L)	0.62±0.115	0.5±0.125	10.786	<0.001
Albumin (3.5-5.3 gm/L)	4.5±1.54	4.6±1.88	0.620	0.535

ALT: alanine aminotransferase

4. Discussion

Systemic hypertension is one of the most common treatable cardiovascular disorders [22]. On the other hand, Hepatitis C is a worldwide problem. Egypt has the highest number of reported infections in the world [23]. Complications of chronic HCV infection are expected to increase over the next few decades [24], placing an ever greater burden on health resources [25]. There are strong evidences to support the notion that HCV predisposes to IR and other metabolic disturbances with their potential consequences such as cardiovascular complications [26]. The present study aimed to evaluate the association between systemic hypertension and chronic HCV-4 infection among Egyptian patients.

The present study revealed a significant higher prevalence of essential HTN among patients with chronic HCV infection. The prevalence of essential HTN among non infected patients was lower than that reported by the Egyptian National hypertension Project [27] and that reported by the Community based survey study on non-communicable diseases and their risk Factors (Epidemiology and Surveillance Unit, Egyptian Ministry of Health and Population in collaboration with the WHO) [28]. This discrepancy is mainly related to the fact that both previous studies included patients with all types of hypertension, either primary or secondary, while the present study excluded all cases of secondary HTN.

The current study revealed a significant higher prevalence of DM among patients with chronic HCV infection. This finding is matching with the report published by Younossi and co-workers who assessed the association of chronic HCV infection with risk factors for cardiovascular diseases using US population data through The National Health and Nutrition Examination Surveys (NHANES). After analyzing the data of 19741 participants, they stated that chronic hepatitis C virus infection is independently associated with presence of metabolic conditions (insulin resistance, type 2 diabetes mellitus and hypertension) and congestive heart failure [12].

The present study also revealed a significant higher prevalence of systemic HTN among patients with chronic HCV infection who had history of DM. This finding strongly supports the notion that HCV predisposes to insulin resistance and possibly other metabolic abnormalities with their potential consequences such as cardiovascular diseases [26]. This finding also supports the suggestion that the elevated prevalence of essential HTN in patients with HCV may occur in parallel with the elevated prevalence of atherosclerosis [29] (as both DM &HTN are important predisposing factors to atherosclerosis).

Approximately 30% of adults are still unaware of their hypertension and up to 40% of patients with hypertension are not receiving treatment [30]. The results of the present study match the internationally reported figures as 30.3% of all hypertensive patients were not aware of their illness. However, the rate of non awareness among patients with HCV infection was significantly lower than that of non infected subjects and this may be largely related to the repeated medical advice seeking and follow up of patients with chronic HCV infection.

All the previous findings emphasize the importance of assessing the true impact of HCV for its hepatic, metabolic and cardiovascular complications. The previous findings have also important clinical and public health implications as the metabolic and cardiovascular complications of HCV can add to the tremendous clinical and economic burden of chronic HCV infection. However, the present study had few limitations. First, atherosclerosis and other cardiovascular complications of chronic HCV infection were not evaluated. Second, neither the hepatic pathological changes (stage of fibrosis, degree of necroinflammation and steatosis) nor the parameters of the metabolic syndrome were evaluated. Third, the degree of glycemic control was not correlated with the grade of hypertension.

5. Conclusion

Significant association exists between chronic HCV-4 infection and systemic hypertension especially among diabetic patients. Patients with chronic HCV infection are more aware of their systemic hypertension than non infected subjects.

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