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Impact of hepatitis C virus on cardiovascular risk among Egyptian patients on maintenance dialysis

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Abstract

Some studies reported the association between cardiovascular disease (CVD) and hepatitis C virus (HCV) with controversial findings. However, almost no study concerned with this issue in Egyptian patients. We aimed to evaluate the association between HCV-infection and CVD development in Egyptian hemodialysis patients and to assess relation between infection and other traditional risk factors. 130 Egyptian dialysis patients (with/without CVD) and 50 healthy sex-matched controls were included. In contrast to patients without CVD (25.3%), HCV positivity rate was significantly (P=0.0001) higher in CVD patients (67.3%). Among all studied parameters, HCV infection was significantly (r=0.415; P=0.0001) correlated with CVD development as well as body mass index, carotid thickening, dialysis duration, decreased high-density lipoproteins, elevated cholesterol, triglycerides, low- and very low-density lipoproteins. Multiple logistic regression analysis revealed that HCV infection (P=0.015) was independently associated with CVD development (OR=5.948, 95 CI (2.7-13.1)). Moreover, HCV-infected patients were significantly associated with all other CVD risk factors. In conclusion, this study highlighted the association between HCV prevalence among Egyptian patients on maintenance hemodialysis and the risk of CVD risk. Thus, further studies are needed to assess the potential role of antiviral treatments using current direct acting antiviral modalities in improving clinical outcome in Egyptian dialysis patients.

Keywords: hepatitis C virus; dialysis patients; cardiovascular risk; lipid alterations.

Abbreviations: CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease; HCV: Hepatitis C Virus; ELISA: Enzyme Linked Immunosorbent Assay.

Introduction

Chronic kidney disease (CKD) patients have an increased risk of mortality especially patients with end-stage renal disease [1]. Remarkably, almost half of deaths are related to CVD and this high mortality give an urge to identify more modifiable risk factors to improve the survival of hemodialysis-dependent patients [2]. In addition to liver disease, chronic infection with HCV has been associated with many extrahepatic comorbidities, including renal disease, CVD, insulin resistance, diabetes mellitus, lymphoproliferative disease and cryoglobulinemia [3]. In dialysis populations, anti-HCV-positive serologic status has been reported to be significantly associated with lower survival [4] and HCV has been included in the modifiable (non-traditional) death risk factors in hemodialysis patients [5].

In contrast to the general population, hemodialysis patients have significantly higher HCV prevalence. This high prevalence is due to transmission by kidney grafts, blood transfusions (before effective HCV screening of blood donors) and nosocomial transmission in dialysis units [6]. Hemodialysis patients with HCV infection have poor vital prognosis due to cirrhosis, CVD and hepatocellular carcinoma. The association between CVD and HCV infection is still an issue of controversy. Some studies have reported higher CVD risk among HCV-infected patients [7] whereas others have not demonstrated such association [8]. HCV role in CVD development was thought to be related to interference with lipid and glucose metabolism that may cause metabolic syndrome development and subsequent risk of developing CVD, type 2 diabetes and insulin resistance. Beyond this, HCV was also thought to increase CVD risk via mechanisms that facilitate endothelial dysfunction and/or chronic inflammation [9, 10]. Almost, there are no studies that assessed the association between HCV infection coexistence and the CVD development in CKD Egyptian patients on maintenance hemodialysis. In this study, we aimed to evaluate the association between HCV infection and CVD development in Egyptian hemodialysis patients and to assess the relation between infection and other traditional CVD risk factors.

Materials and methods

Patients

Participants were 130 Egyptian CKD patients who were receiving thrice weekly chronic hemodialysis. Mean age was 50.0 ± 10.5 years and there were 69 males and 61 females. Eligible patients were women and men, >18 years old, who were undergoing hemodialysis. HCV patients with liver cirrhosis or patients with any other chronic diseases or cancers were not eligible. In addition, 50 healthy sex-matched individuals were enrolled as controls. Retrospectively, patient's data were recorded from medical files of each patient. This study was designed according to Helsinki Declaration ethical guidelines.

Laboratory and biomarker measurements

Blood samples were collected and centrifuged at 1000 ×g for 15 minutes and stored at −20°C until analysis. Using fresh serum, kidney and liver function tests and lipid profile were measured on fully automated Biochemistry analyzer (Response 920, Diasys Diagnostic Systems, GmbH, Germany) and minerals were determined using blood gas/electrolyte analyzer (GEM Premier 3000, Werfen, Belgium). KEDTA treated blood was used for complete blood count on automated hematology analyzer (Phoenix NCC-3300, NeoMedica Bioscience Technology, Serbia). HCV antibodies were detected by using commercial ELISA kits (abia HCV-Ab, AB Diagnostic Systems, GmbH, Germany).

Statistical analysis

Data analysis was performed using GraphPad Prism (*v.* 6) and SPSS (*v.* 20) software. Normally and non-normally distributed data are shown as mean ± standard deviation (SD) and median (interquartile range), respectively. *ANOVA* and student *t* test were used to compare values between groups with normal distribution. In case of skewed variable distribution, Kruskal-Wallis test was used. Proportions in groups were compared using Pearson $\chi 2$ test. $P<0.05$ was considered statistically significant. Multiple logistic regression was used to estimate HCV odd ratio (OR) and 95% confidence intervals (95% CIs) for CVD development. Spearman's rank correlation analysis was used to assess the association between any two variables.

Table 1: Patient's characteristics.

Parameter	Healthy	Hemodialysis patients		*P* value
		Without CVD	With CVD	
Number	50	75	55	-
Age (Years)	35.6 ± 10.5	39.6 ± 11.8	59.9 ± 13.7	0.0351
Gender (male/female)	30/20	40/35	29/26	0.409
BMI	21.5 ± 3.7	22.1 ± 3.7	28.7 ± 4.9	<0.0001
Pre-dialysis creatinine (mg/dL)	0.7 ± 0.1	9.53 ± 2.8	9.65 ± 3.5	<0.0001
Post-dialysis creatinine (mg/dL)	-	2.9 ± 1.0	3.4 ± 1.2	0.364
Pre-dialysis urea (mg/dL)	20.0 ± 2.64	140.0 ± 39.0	130.4 ± 38.0	<0.0001
Post-dialysis urea (mg/dL)	-	44.2 ± 10.5	43.2 ± 11.0	0.825
Uric acid (mg/dL)	3.5 ± 1.4	5.4 ± 1.9	6.6 ± 1.9	<0.0001
ALT (U/L)	20.1 ± 1.4	33.3 ± 9.5	35.3 ± 10.0	0.045

AST (U/L)	19.2 ± 3.3	29.2 ± 9.9	35.0 ± 8.9	0.047
Albumin (g/dL)	4.3 ± 0.53	3.6 ± 0.50	3.5 ± 0.25	0.002
Bilirubin (mg/dL)	0.7 ± 0.1	0.8 ± 0.1	1.0 ± 0.15	0.048
Sodium (mmol/L)	131.7 ± 1.58	137.9 ± 3.65	138.3 ± 3.63	0.0851
Potassium (mmol/L)	3.95 ± 0.56	4.76 ± 1.18	4.76 ± 1.40	0.0914
Dialysis duration (Years)	-	2.8 ± 1.5	6.2 ± 2.5	<0.0001
Carotid intima thickness (mm)	0.73 ± 0.02	1.23 ± 0.02	1.51 ± 0.08	<0.0001
Cholesterol (mg/dL)	150.0 ± 35.6	164.0 ± 47.6	196.1 ± 60.0	<0.0001
Triglycerides (mg/dL)	99 (53-125)	129 (99-160)	140 (111-200)	0.0589
HDL (mg/dL)	57 (47-69)	50 (35-76)	15 (9-30)	<0.0001
LDL (mg/dL)	44 (20-52)	65 (31-110)	110 (98-185)	<0.0001
vLDL (mg/dL)	22 (12-24)	30 (20-35)	40 (30-50)	0.0025
Hemoglobin (g/dL)	12.0 ± 2.1	10.0 ± 1.8	9.7 ± 1.7	0.042
White blood cells (10^9/L)	5.5 ± 1.8	6.4 ± 2.2	5.6 ± 2.0	0.156
Red blood cells (10^{12}/L)	4.0 ± 0.92	3.5 ± 0.80	3.6 ± 0.73	0.025
Platelets (10^9/L)	200.79 ± 55.21	152.88 ± 40.51	145.82 ± 50.51	0.034

Abbreviations: BMI: Body Mass Index; ALT, AST: Alanine And Aspartate Aminotransferases; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; VLDL: Very High-Density Lipoprotein. Normally distributed variables were expressed as mean±SD. Non-normally distributed variables were expressed as median (interquartile range). Significant difference was determined using X^2 test, ANOVA and Kruskal-Wallis tests as appropriate. $P<0.05$ was considered significant.

Factors associated with CVD

Among all studied parameters, CVD development was significantly ($P<0.05$) correlated with increased body mass index, carotid thickening, long dialysis duration, decreased high-density lipoproteins, elevated cholesterol, triglycerides, low- and very low-density lipoproteins and HCV infection ($r=0.415$; $P=0.0001$) (Table 2).

Table 2: Correlation between CVD development and other clinical risk factors.

Factor correlated with HCV-infection	Correlation coefficient (*r*)	*P* value
Body mass index	0.550	0.0001
Carotid thickness (mm)	0.425	0.0001
Dialysis duration (Years)	0.645	0.0001
Cholesterol (mg/dL)	0.262	0.005
Triglycerides (mg/dL)	0.203	0.035
HDL (mg/dL)	-0.821	0.0001
LDL (mg/dL)	0.522	0.0001
vLDL (mg/dL)	0.350	0.0001
HCV-infection	0.415	0.0001

Abbreviations: CVD: Cardiovascular Diseases; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; VLDL: Very High-Density Lipoprotein.

Table 3: Parameters independently associated with CVD development.

Factor	Beta	Standard error	95% CI for Beta	*P* Value
Body mass index	0.012	0.008	-0.004 - 0.028	0.153
Carotid thickness (mm)	0.017	0.009	0.008 - 0.032	0.002
Dialysis duration (Years)	0.037	0.013	0.011 - 0.064	0.006
Cholesterol (mg/dL)	0.000	0.001	-0.001 - 0.002	0.664
Triglycerides (mg/dL)	-0.002	0.001	-0.004 - 0.000	0.057
HDL (mg/dL)	-0.009	0.001	-0.012 - -0.006	0.0001
LDL (mg/dL)	0.000	0.001	-0.001 - 0.002	0.576
vLDL (mg/dL)	0.001	0.005	0.004 - 0.022	0.056
HCV-infection	0.104	0.062	0.031 – 0.278	0.015

Abbreviations: CVD: Cardiovascular Diseases; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; VLDL: Very High-Density Lipoprotein.

Results

Characteristics of patients: Demographic and clinical characteristics of patients and controls were summarized in (Table 1). Hemodialysis patients with CVD were older ($P=0.0351$) than patients without CVD and healthy controls. Besides creatinine and urea blood levels, hemodialysis patients were associated with elevated levels of uric acid, sodium and potassium and decreased level of albumin. They also had overweight and microcytic anemia. Patients with CVD were associated with long dialysis duration, carotid intima thickening and dyslipidemia, including decreased levels of high-density lipoprotein and elevated levels of cholesterol, triglycerides, low density lipoprotein and very low-density lipoprotein.

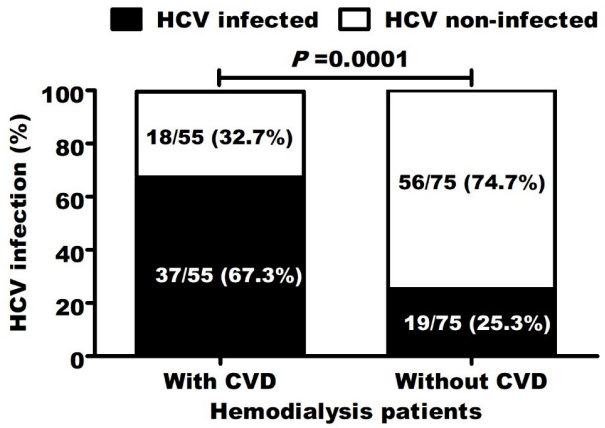

Figure 1: HCV positivity in dialysis patients with and without CVD. X2 test revealed that HCV was more prevalent in patients with CVD.

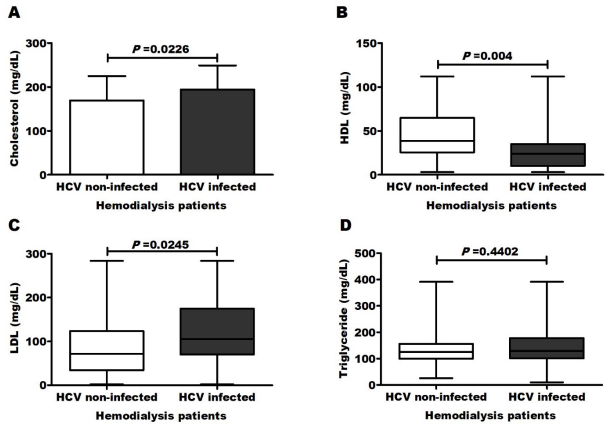

Figure 2: Lipid alterations in dialysis patients with HCV infection. Significant differences were assesed by student t test and Kruskal-Wallis test appropriately.

HCV infection independently associated with CVD

Screening for HCV infection showed that 37/55 (67.3%) of patients with CVD and 19/75 (25.3%) of patients without CVD were anti-HCV-positive. The positivity rate was significantly (*P*=0.0001) higher in CVD patients (Figure 1). In multiple logistic regression analysis, only HCV infection (*P*=0.015) as well as carotid thickening (*P*=0.002), long dialysis duration (*P*=0.006) and decreased high-density lipoproteins (*P*=0.001) still significantly related to CVD development. The odd ratio (OR=5.948, 95 CI (2.7-13.1), *P*<0.0001) for CVD increased in patients with HCV infection compared to uninfected patients. Moreover, HCV-infected patients were significantly associated with all other CVD risk factors (Figure 2 and Table 4).

Table 4: Correlation between HCV-infection and CVD related clinical risk factors.

Factor correlated with HCV-infection	Correlation coefficient (*r*)	*P* value
CVD development	0.415	0.0001
Body mass index	0.596	0.0001
Carotid thickness (mm)	0.326	0.0001
Dialysis duration (Years)	0.387	0.0001
Cholesterol (mg/dL)	0.254	0.010
Triglycerides (mg/dL)	0.112	0.249
HDL (mg/dL)	-0.375	0.0001
LDL (mg/dL)	0.245	0.015
vLDL (mg/dL)	0.172	0.073

Abbreviations: CVD: Cardiovascular Diseases; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; VLDL: Very High-Density Lipoprotein.

Discussion

Despite HCV prevalence reduction, hemodialysis patients still comprise a high risk group [11]. In hemodialysis population, true HCV impact on survival is difficult to assess and these patients may die from other causes, mainly CVD, before developing liver cirrhosis or hepatoceluular carcinoma [11]. It stills unclear whether elevated mortality risk in HCV infected patients on hemodialysis is related only to a higher rate of liver-related diseases or to another comorbidities in HCV-infected patients on dialysis [12]. Here, we aimed to evaluate the prevelance of CVD in Egyptian hemodialysis patients with and without HCV-infection. Also, we aimed to assess the relation between HCV infection and CVD traditional risk factors including interference with lipids.

Here and among all studied parameters, CVD development was significantly correlated with HCV infection (*r*=0.415; *P*=0.0001) as well as other CVD traditional risk factors in dialysis patients including increased body mass index [13], carotid thickening [14], long dialysis duration [15] and lipid alterations including decreased high-density lipoproteins and elevated cholesterol, triglycerides, low- and very low-density lipoproteins [16]. Compared to uninfected patients (25.3%), high percentage (67.3%) of HCV-infected patients was with CVD.

HCV infection results in systemic and hepatic inflammation and it has been suggested that indirect and direct mechanisms can be involved CVD development *via* inducing pro-atherogenic metabolic factors and increased levels of pro-atherogenic cytokines and chemokines [17]. Carefully, the relationships between immune response to HCV infection and CVD have been examined [18]. In contrast to uninfected patients, patients with HCV infection were associated with higher TNF-α level [18], more pronounced intima-media thickness [19], higher levels of proinflammatory cytokines and ratio of proinflammatory/anti-inflammatory cytokines [20] and higher risk of cardiac failure and death [18]. Also, cryoglobulinemia occurs in many HCV infected patients and the presence of cryoglobulinemia is associated with cardiovascular and vasculitis events [21]. Besides HCV role in chronic inflammation development involving the arteries, sequences of HCV-RNA have been detected within carotid plaques, suggesting consequent local pro-atherogenic action [17].

In this study, multiple logistic regressions, that adjusted other demographic and clinical characteristics, revealed that HCV infection (*P*=0.015) was independently related to CVD development [OR=5.948, 95 CI (2.7-13.1)]. Interestingly, HCV-infected patients were significantly associated with other CVD risk factors including increased body mass index, carotid thickening, long dialysis duration and dyslipidaemia.

After adjustment for several covariates including age, diabetes mellitus, dialysis vintage, gender, age and others, the persistence of an increased HCV-associated CVD risk was observed [12]. In HCV infected hemodialysis patients (n=2,778), Kalantar-Zadeh et al. were the first researchers to establish greater CVD risk. After adjustment for case-mix and measures of malnutrition-inflammation complex syndrome, they report-

ed that HCV positivity among patients <65 years was associated with 40-80% higher hazard ratio of cardiovascular death [22]. Other study on a large cohort of HCV-infected patients treated with haemo- and peritoneal dialysis found that coronary artery disease was an independent mortality risk factor [23, 24]. In patients undergoing regular dialysis, coronary flow reserve was significantly lower in HCV-infected than uninfected patients [25]. By multiple logistic regression analysis, Oyake et al. found that mean blood pressure and HCV infection were significantly and independently associated with high aortic pulse wave velocity [26]. In accordance with our findings, HCV infection was reported to be associated with traditional CVD risk factors including body mass index [27], carotid intima-media thickening [28] and dyslipidaemia [29].

Conclusions

In conclusion, this study highlighted the association between the prevalence of HCV and CVD risk and its related risk factors among Egyptian patients on maintenance hemodialysis. These results may have implications not only in HCV management in these patients but it shed the light on the potential role of anti-HCV treatment using current direct acting antiviral modalities in improving clinical outcome in Egyptian dialysis patients.

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