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Research article

Prevalence of hepatitis C and diabetes among chronic kidney diseases patients and their effects on renal functions

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Key words: Chronic kidney diseases, CKD, HCV, Diabetes, Renal functions.

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Abstract

Background: The prevalence of hepatitis C virus infection in developed countries is higher in patients undergoing dialysis and in patients with chronic kidney disease (CKD) than the general population. The hepatitis C virus mainly causes liver damage, but is also associated with extra-hepatic diseases, including various types of glomerulonephritis. Diabetic nephropathy is one of the most common complications of diabetes. The prevalence of diabetic nephropathy is increasing steeply along with the diabetes epidemic. **Objective:** This study aimed to discover the effects of HCV infection and diabetes in the progression of CKD. **Methods:** This study was conducted on 72 patients with chronic renal failure and 40 healthy persons as control. The study was performed in El-Zahraa hospital, Libya. **Results:** Most of patients were in stage five of CKD. By serological test for HCV, we found that, 31.1% of male and 28.9% of female patients are infected with hepatitis C virus and 48.75% of males and 42.1% of females were diabetic. The diabetic patients who infected with HCV were 14.3% of males and 26.3% of females. The patients who free from both diabetes and HCV were 20% of males and 20.3% of females. The diabetic patients showed also increase in serum creatinine, which is higher than the increase in the groups free from HCV and diabetes but lower than the groups of HCV infection, also urea levels in both diabetic and hepatitis groups were higher than levels in non-diabetic and negative for HCV serological test.

Introduction

The prevalence of hepatitis C virus (HCV) infection in developed countries is higher in patients undergoing dialysis and in patients with chronic kidney disease (CKD) than the general population [1]. CKD is an increasing public health problem worldwide. The well-recognized risk factors for CKD are advanced age, diabetes, hypertension, hyperlipidemia, coronary heart disease, and cirrhosis. Infectious disease is a recently identified and under-recognized risk factor for CKD. Hepatitis C has a high prevalence and affects about 170 million people worldwide. The hepatitis C virus (HCV) mainly causes liver damage, but is also associated with extra-hepatic diseases, including various types of glomerulonephritis, even in the absence of cirrhosis. In addition, HCV is more common in CKD patients who are not yet on dialysis than in the general population. HCV infection leads to a rapid decline in the renal function of patients with diabetic nephropathy and of HCV-infected patients with cirrhosis who terminated interferon therapy. Collectively, the studies suggested that HCV infection has an adverse impact on renal function [2].

Chronic HCV infection can potentially cause chronic kidney diseases. Both glomerular and tubulointerstitial diseases associated with HCV have been described. However, the exact mechanism of these diseases is unclear. An association between HCV infection and albuminuria without overt kidney disease has also been described; hence, HCV infection may have a greater influence on renal dysfunction than is presently documented. The most common renal manifestations of HCV infection are essential mixed cryoglobulinemia leading to membrano proliferative glomerulonephritis (MPGN), MPGN without cryoglobulinemia, and membranous glomerulonephritis. On the other hand, patients with end-stage kidney disease are at an increased risk of acquiring HCV infection due to their frequent

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exposure to potentially contaminated devices in dialysis units and their long-term use of vascular access [3].

Liver disease related to HCV infection is a significant cause of morbidity and mortality in hemodialysis patients and kidney transplant recipients. In developed countries, the prevalence of anti-HCV seropositivity among patients on maintenance hemodialysis ranges between 5% and 60%. Patients on hemodialysis are at high risk for HCV, with frequency of infection several times higher than that in non-uremic patients. The spread of HCV in hemodialysis units is declining, but the prevalence of HCV in hemodialysis patients remains high. Several observational studies have demonstrated a significant and independent relationship between anti-HCV seropositive status and lower survival rate in patients with end-stage renal disease [4].

Lee *et al.,* [5] identified HCV infection as an independent risk factor for the transition from chronic kidney disease to end-stage renal disease. A meta-analysis by Fabrizi *et al.*, [6] revealed that hemodialysis can negatively modify the course of HCV infection. The authors found that the estimated relative risk of liver-related mortality in anti-HCV-positive patients on hemodialysis was 1.57 times than that observed for anti-HCV-negative counterparts. The authors concluded that, in hemodialysis patients, the presence of anti-HCV antibodies is an independent risk factor for death, because of increased risk of cirrhosis and hepato-cellular carcinoma.

Diabetes causes significant morbidity, disability and early mortality. Diabetes has been identified as a major contributor in several other important diseases, both non-communicable diseases such as cardiovascular disease and renal disease, and communicable diseases such as invasive bacterial infections. Diabetic nephropathy is one of the most common complications of diabetes. The prevalence of diabetic nephropathy is increasing steeply along with the diabetes epidemic [7]. Approximately one third to half of patients with diabetes develops renal manifestations. Diabetic nephropathy is associated with increased premature mortality, end-stage renal disease and need to renal replacement therapy, cardiovascular diseases, and escalating health-care costs [8]. This study aimed to discover the effects of HCV infection and diabetes in the progression of chronic kidney disease.

Experimental

This study was conducted on 72 patients (35 males and 37 females) with chronic renal failure from January to June 2013 and a group of 40 (20 males and 20 females) individuals as control. Ethical approve and patients consent statement were taken from everyone and the study was performed in El-Zahraa hospital in the west of Libya. At first, all patients with proven chronic renal failure were included in study. In order to eliminate effects of sex and age on comparison between cases and control groups, age and sex were selected in each pair of groups as similar as possible. Demographic and anthropometric data including age, sex, weight, height, BMI and blood pressure were measured for the participants. All patients and normal participants were Libyans, above 18 years of age, and free from chronic degenerative diseases such as cancer or peritonitis.

Five mL of blood was drawn by venous puncture. Collected blood sample was emptied in plain vial for biochemical tests. After clotting of blood in the plain vial, serum was separated, within an hour; by centrifugation at 3000 - 5000 g for 5 min. Serum was used for measurements of urea, creatinine and glucose levels, serum was also used for serological diagnosis of HCV. Laboratory standard operation procedures were maintained for all laboratory analysis. Internal quality control sera, both normal and pathological, were also run for each lot of the test, for the validation of the results. Biochemical studies were performed using commercially available kits from Biomeriux (France), and serum levels of creatinine, urea, and glucose were quantified according to the manufacturer's instructions.

Defining variables

CKD was defined as reduced excretory function with an estimated GFR (eGFR) <60 mL/min/1.73 m^2 as a marker of kidney dysfunction. Furthermore, CKD was defined and classified into five stages of CKD as per National Kidney Foundation guidelines. The formula of Cockcroft and Gault equation was used to calculate eGFR[9].

eGFR (in male) = [140 - age (in years)] x weight (in kg) /[72 x serum creatinine (mg/dl)]

A companion equation for women, based on their 15% lower muscle mass (on average):

eGFR (in female)= [140 - age (in years)] x weight (in kg) x0.85 / [72 x serum creatinine (mg/dl)]

Statistical analysis

The data was analyzed by using Excel 2010, and graph Pad Prism software version 5. Comparison of mean value of continuous data was tested by t test and ANOVA test. p-value of <0.05 was used to establish statistical significance.

Results and Discussion

Results

The patients of this study are 35 males and 37 females were diagnosed as chronic kidney disease patients by physical and laboratory investigations. By estimating GFR, most of patients were in stage five of chronic kidney disease, as illustrated in figure (1), 80% of males and 75.6 of female were within this stage. The patients who within stage four limits are 17.1% for males and 18.9% for females, but there is very low percentage of patients who within stage three limits (2.9% for males and 5.5 for females), on the other hand, no patients within limits of stages one or two.

By serological test for HCV, we found that, 31.1% of male and 28.9% of female patients are infected with hepatitis C virus. On measuring fasting blood sugar for patient groups, we found that, 48.75% of male and 42.1% of female patients were diabetic. The diabetic patients who infected with HCV were 14.3% of males and 26.3% of females. The patients who free from both diabetes and HCV were 20% of males and 20.3% of females as illustrated in figure (2).

The illustrated results in table 1 shows the changes in creatinine and urea concentrations in serum and the estimated GFR in infected patients with HCV, diabetic patients, combined infected with HCV and diabetic, and patients who free from both diabetes and HCV, all these groups were compared to healthy person results in both genders. Serum creatinine results showed highly significant increase in all patient groups compared to healthy persons. The CKD patients who free from HCV and diabetes, showed increase in serum creatinine by 1036% and 983% for males and females respectively, compared to healthy group, on the other hand the increase in patients who infected with HCV was 1377% and 1566% for males and females respectively on comparing with the control groups for each gender. The diabetic patients showed also increase in serum creatinine, which is higher than the increase in the groups free from HCV and diabetes but lower than the groups of HCV infection, the percentage of increase in these groups were 1150% and 1427% for males and females respectively, compared to control. The groups of patients who infected with HCV and also diabetic, showed increase in serum creatinine by 1377% and 1566% for males and females respectively, on comparing to control as illustrated in table 1.

Serum urea concentrations in all patient groups also showed dramatic increase compared to healthy persons. The urea levels in groups who free from HCV and diabetes were increased by 604% and 300% in males and females respectively, on the other hand, this parameter was increased in HCV infected groups by 550% and 642% for male and female patients, and 616% and 588% in diabetic male and female patients respectively. The patients who have combined HCV infection and diabetes were showed increase in urea levels by 650% and 642% for male and female patients respectively compared to their corresponding healthy groups (Table 1).

Estimated GFR in all patient groups showed highly significant decrease compared to healthy persons. The illustrated data in table (1) showed that, the patient groups who free from diabetes and HCV were complained from reduction of GFR by -87.6% and -87.7% in male and female patient groups respectively, but the results of the groups who infected with HCV were decreased by -91% and -92% for male and females, the results of diabetic groups were reduced by -90 and -91.8% for male and female patient groups. The results of combined HCV and diabetes groups were reduced by -91% and -92% in male and female patient groups respectively compared to corresponding control group.

Discussion

This study allowed us to uncover a series of important facts. We were able to identify that there is a significant association between HCV infection and diabetes mellitus in one hand and progression of renal failure in the other hand. Our study showed that the percentage of patients with CKD and infected with HCV were 31.5% of males and 29% of females. Serologic testing has clearly demonstrated that HCV infection is highly prevalent among end stage renal disease (ESRD) patients and is a serious cause of increased morbidity and mortality in this group. Failures of HCV screening, excessive exposure to blood and blood products, nosocomial transmission of HCV in hemodialysis units, and long dialysis duration are the main determinants of increased risk of HCV infection in the hemodialysis patient group [4,10]. Molecular studies have shown that the HCV core protein directly inhibits insulin signaling and increases oxidative stress, which can exacerbate insulin resistance [11] and potentially lead to metabolic syndrome and advanced cirrhosis [12].

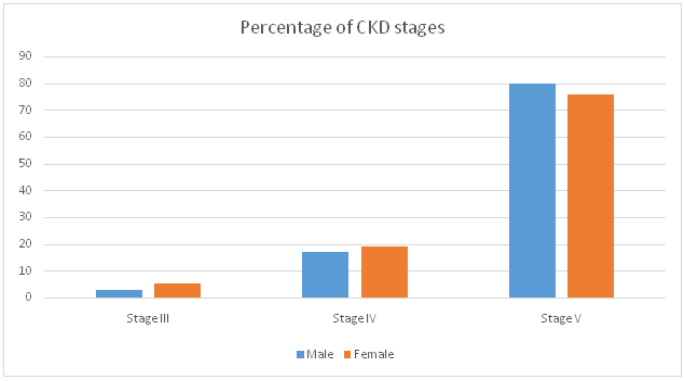


Figure 1. Percentages of CKD stages among patients

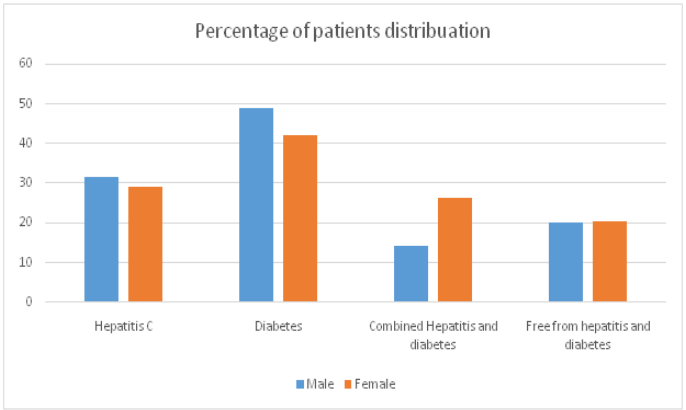


Figure 2. Distribution of patient groups according to HCV and diabetic status

Table 1. Renal function tests as affected by Diabetes and HCV in chronic kidney diseases patients

Gender		Male					Female				
Parameter		Control	HCV	Diabetes	Combined HCV and diabetes	Free from HCV and diabetes	Control	HCV	Diabetes	Combined HCV and diabetes	Free from HCV and diabetes
Serum Creatinine (mg/dl)	Mean ± SD	0.88 ± 0.15	13 ± 2.2	11 ± 3.6	13 ± 1.8	10 ± 2.9	0.72 ± 0.13	12 ± 2.6	11 ± 2.2	12 ± 2.6	7.8 ± 1.7
	% of difference		1377%	1150%	1377%	1036%		1566%	1427%	1566%	983%
Serum Urea (mg/dl)	Mean ± SD	24 ± 4.5	156 ± 54	172 ± 54	180 ± 40	169 ± 64	26 ± 3.6	193 ± 27	179 ± 30	193 ± 27	104 ± 27
	% of difference		550%	616%	650%	604%		642%	588%	642%	300%
eGFR ml/min	Mean ± SD	121 ± 10	11 ± 6.4	12 ± 5.3	11 ± 6.7	15 ± 4.7	122 ± 8.4	9.8 ± 3.0	10 ± 2.5	9.8 ± 3.0	15 ± 7.9
	% of difference		-91%	-90%	-91%	-87.6%		-92%	-91.8%	-92%	-87.7%

Insulin resistance and oxidative stress can also lead to endothelial dysfunction and is implicated in the progression of CKD [2, 13]. These molecular studies provide a biological basis for the hypothesis that HCV infection increases the risk for CKD. The natural course of HCV infection in patients on HD is not well understood, although there is evidence showing that HCV seropositivity can definitely reduce the overall outcomes in these patients. The reason for HCV viral load reduction in HD patients is unclear. HCV infection naturally causes liver injury by immunologic reactions rather than via a direct cytopathic effect on hepatocytes. It has been postulated that HD patients are, in general, immuno-compromised, and this immuno-compromised state could be a possible cause of diminished inflammatory reactions
and reduced hepatocyte destruction by HCV [3]. In the present study, 14.3% of male patients and 26.3% of female patients were diabetic and infected with HCV, this will raise the question if there exists a specific link between this type of hepatitis virus and diabetes and if hepatitis C virus represents a risk factor for the development of diabetes. Some authors stated that there is a connection between diabetes mellitus and the progression of the chronic liver disease to hepatocellular carcinoma.

Although kidney damage may take many forms in the context of chronic liver injury, the most frequent type of renal disease that we found was represented by glomerulonephritis. Glomerular injury was the most common type of renal damage both in the hepatitis patients and in those with cirrhosis. Glomerular injury was strongly correlated with the presence of HCV than with HBV, both in patients with chronic viral hepatitis and liver cirrhosis [14].

In this study we found that 48.75% of male patients and 42.1% of female patients were diabetic. Several mechanisms underlying the pathogenesis of diabetic nephropathy have been suggested and include glomerular hyperfiltration; hyperglycemia and the increased production of advanced glycation end products; hypoxia-inflammation and the activation of cytokines. Hyperfiltration commonly occur in early in the course of diabetes and involves glucose-dependent dilation of the afferent arteriolar dilation, and the enhanced filtration area secondary to the increase in the number of mesangial cells and capillary loops [7].

Molecular level action involves vasoactive mediators like insulin-like growth factor 1, transforming growth factor beta, nitric oxide, prostaglandin, glucagon and vascular endothelial growth factor. Other hallmarks of diabetic nephropathy include nodular diabetic glomerulosclerosis and diffuse glomerulosclerosis, mediated at least in part by inflammatory processes and immune cells activity [15]. Interstitial fibrosis and tubular atrophy are also seen early in DN, with the underlying pathogenetic mechanism being similar to those in progressive non diabetic renal disease [16].

Conclusion

This study concluded that the prevalence of hepatitis C and diabetes among chronic kidney diseases is high and their effects on renal functions are observable.

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