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Original Article

Nephropathy and Neuropathy in Diabetic Patients with Chronic Hepatitis C Virus Infection

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Abstract

Introduction: Several reports described an association between type 2 diabetes mellitus (DM) and chronic hepatitis C virus (HCV) infection. Chronic HCV infection is prevalent in Egypt. The present work aimed to evaluate the prevalence of proteinuria and neuropathy among diabetic patients with and without chronic HCV infection

Methods: A total of 70 diabetic patients were recruited from patients that attended the outpatient clinic of Mansoura Specialized Medical University Hospital. They were evaluated for diabetic retinopathy, peripheral neuropathy, autonomic neuropathy, high blood pressure, urinary albumin excretion (UAE), serum creatinine, lipid profile and assay of HCV-RNA.

Results: The prevalence of HCV infection among this group of diabetic patients was 35.7% compared to 10% in a matched control group ($P< 0.05$). Diabetic patients with chronic HCV infection (n=45) and diabetic patients without HCV infection (n=25) had no significant differences in diabetes type, diabetes duration, prevalence of hypertension, level of glycosylated hemoglobin or prevalence of diabetic retinopathy. The prevalence of macroalbuminuria, peripheral neuropathy and autonomic neuropahty was higher among diabetic patients with chronic HCV infection ($P < 0.05$). Also, diabetic patients with chronic HCV infection had higher mean arterial pressure, higher serum creatinine, higher triglyceride and cholesterol levels, and higher UAE ($P < 0.05$).

Conclusion: A high prevalence of HCV infection is observed among this group of Egyptian diabetic patients, and it was associated with higher rates of nephropathy and peripheral neuropathy compared to diabetic patients without HCV infection.

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Key words: Diabetes mellitus; Egypt; HCV infection; Nephropathy; Neuropahty; Retinopathy

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Introduction

The prevalence of diabetes mellitus (DM) and its complications is increasing worldwide. Vascular complications of DM are a common cause of mortality and morbidity in diabetics and constitute the major clinical burden of the disease. Type 1 and type 2 diabetes have distinct etiologies, but patients with either disease are at risk of developing the same range of microvascular and macrovascular complications including nephropathy, neuropathy, retinopathy and atherosclerosis.

Throughout the world, the number of patients requiring hemodialysis for diabetic nephropathy has increased enormously [1]. Although several factors, such as poor glycemic control, high blood pressure, proteinuria, lipid abnormalities, and genetic predisposition were identified as contributing to the progression of diabetic nephropathy, it is highly suspected that there may be other unidentified factors.

Hepatitis C virus (HCV) is both a cause and a complication of chronic renal disease. Chronic infection with HCV can lead to the immune complex syndromes of cryoglobulinemia and membranoproliferative glomerulonephritis (MPGN). Lymphoproliferative disorders, Sjogren syndrome, porphyria cutanea tarda, and neuropathies are other extrahepatic manifestations of HCV infection. The pathophysiologic basis for most of these syndromes seems immunologic [2].

Several reports described an association between type 2 diabetes and chronic HCV infection. Type 2 diabetes was reported to be commoner in patients with chronic HCV infection [3-6], indicating that HCV may promote the development of type 2 diabetes in susceptible individuals. Hepatic steatosis and cirrhosis, both features

Table 1: Clinical and biochemical characteristics of the study patients

Clinical and biochemical characteristics	Value
DM type 1, number (%)	17 (24.3%)
DM type 2, number (%)	53 (75.7%)
Peripheral neuropathy, number (%)	40 (57.2%)
Autonomic neuropahty, number (%)	11 (15.7%)
Nephropathy, number (%)	29 (41.4%)
Retinopathy, number (%)	20 (28.6%)
Hypertension, number (%)	22 (31.4%)
MAP mmHg, mean ± SD	100 ± 15
Serum creatinine (mg/dl), mean ± SD	0.95 ± 0.1
Serum triglycerides (mg/dl), mean ± SD	119 ± 36
Serum cholesterol (mg/dl), mean ± SD	195 ± 35
HbA1c (%), mean ± SD	8.2 ± 2.5
Creatinine clearance (ml/min), mean ± SD	126 ± 31
UAE (mcg/ml), mean ± SD	64 ± 59

MAP: mean arterial pressure; HA1c: glycosylated hemoglobin; UAE: urinary albumin excretion.

of chronic HCV infection, have been associated with abnormal glucose regulation and insulin resistance [7]. Interestingly, a high prevalence of HCV infection was reported in diabetic patients [8].

Chronic HCV infection is prevalent in Egypt. In a study of 55,922 potentially healthy asymptomatic blood donors screened between 2000 and 2007, the cumulative seroprevalence of HCV infection was 12% [9].

The present work aimed to study the prevalence of HCV infection among a group of Egyptian diabetic patients, and to evaluate the prevalence of proteinuria and neuropathy among diabetic patients with and without chronic HCV infection.

Methods

A total of 70 diabetic patients were recruited from patients that attended the outpatient clinic of diabetes and endocrine unit, Mansoura Specialized Medical University Hospital, in the summer months of 2005. This included 15 patients with type 1 diabetes and 55 patients with type 2 diabetes mellitus. Thirty normal healthy volunteers, of matched age and sex were taken as a control group. None of the studied cases had a history of previous cardiac, pulmonary, renal or endocrine disorders other than diabetes mellitus.

Diabetic patients were evaluated for evidence of diabetic retinopathy, peripheral neuropathy, autonomic neuropathy, high blood pressure (BP) and cardiovascular status. Investigations included urinary albumin excretion (UAE), serum creatinine, lipid profile and assay of HCV-RNA. Urinary albumin concentration was measured by radioimmunoassay. Urine samples were stored at -20°C and thawed once before measurement. The inter- and intra-assay coefficients of variation for UAE were 11 and 4% respectively. Assay of HCV-RNA by polymerase chain reaction (PCR) was carried out on frozen samples using ultraspec kit (Biotecx Laboratories Inc. 6023 South Loop East, Houston, Texas 77033. USA). Peripheral neuropathy was diagnosed based on neuropathic symptoms and impaired vibration sense. Autonomic neuropathy was diagnosed by the presence of postural hypotension. Nephropathy was diagnosed by the presence of persistent albuminuria of 20 to 200 mg/24 hours (microalbuminuria) in at least three occasions in the absence of urinary tract infection. Macroalbuminuria was diagnosed when persistent albuminuria ≥ 300 mg/24 hours was found. Chi square test was used to compare proportions. Student-t test was used to compare means. P value < 0.05 was considered statistically significant.

Results

The study group included 20 males and 50 females, with a mean age of 47±18 years. The control group consisted of nine males and 21 females with a mean age of 45±13 years. None of the patients tested positive for HBV infection. The prevalence of HCV infection among diabetic patients was 35.7% compared to 10% in the control group (P< 0.05). The clinical characteristics of the diabetic patients are described (Table 1).

Diabetic patients with chronic HCV infection (n = 45) and diabetic patients without HCV infection (n = 25) had no significant differences in diabetes type, diabetes duration, prevalence of hypertension, or level of glycosylated hemoglobin. Diabetic retinopathy was not significantly different between the two groups (Table 2).

The prevalence of macroalbuminuria, peripheral neuropathy and autonomic neuropahty was higher among diabetic patients with chronic HCV infection. Also, diabetic patients with chronic HCV infection had higher mean arterial pressure, higher serum creatinine, higher triglyceride and cholesterol levels, and higher UAE (Table 2).

Nephropathic patients with and without HCV infection were not different regarding diabetic duration, mean arterial pressure or HbA1c level. However, nephropathic patients with HCV infection were less likely to have diabetic retinopathy (Table 3).

Table 2: Comparison of diabetic patients with and without HCV infection

Clinical and biochemical characteristics	HCV negative group (n=45)	HCV positive group (n=25)
Diabetic duration (months), mean ± SD	94 ± 55	101 ± 78
DM type 1, number (%)	12 (27)	5 (20)
DM type 2, number (%)	33 (73)	20 (80)
Hypertension, number (%)	13 (28.9)	9 (36)
MAP (mmHg), mean ± SD	93 ± 15	104 ± 6*
Nephropathy, number (%)	15 (33.3)	14 (56)*
Microalbuminuria, number (%)	10 (22.2)	8 (32)
Macroalbuminuria, number (%)	5 (11.1)	6 (24)*
Diabetic retinopathy, number (%)	11 (24.4)	9 (36)
Background diabetic retinopathy (%)	6 (13.3)	4 (16)
Proliferative diabetic retinopathy (%)	5 (11.1)	5 (20)*
Peripheral neuropathy, number (%)	21 (46.7)	19 (76)*
Autonomic neuropathy, number (%)	5 (11.1)	6 (24)*
Serum creatinine (mg/dl), mean ± SD	0.81 ± 0.11	0.97 ± 0.12*
Serum triglycerides (mg/dl), mean ± SD	109 ± 33	123 ± 36*
Serum cholesterol (mg/dl), mean ± SD	166 ± 32	195 ± 36*
HbA1c (%), mean ± SD	7.9 ± 2.2	8.3 ± 2.3
Creatinine clearance (ml/min), mean ± SD	111 ± 21	121 ± 23
UAE (mcg/ml), mean ± SD	43 ± 35	111 ± 79*

MAP: mean arterial pressure; HbA1c: glycosylated hemoglobin; UAE: urinary albumin excretion
* $P < 0.05$

Discussion

Both HCV infection and diabetes are common health problems in Egypt. HCV infection is known to have a wide variety of manifestations in the kidney. The direct effects of HCV infection on the kidney include membranous nephropathy, cryoglobulinemia, and membranoproliferative glomerulonephritis (MPGN). The presence of HCV worsens the progression of several renal diseases, and it is more prevalent in patients with type 2 diabetic nephropathy [8]. Therefore, it is possible that HCV contributes to the progression of renal disease in diabetic patients [10, 11].

In the present study, prevalence rate of HCV infection among a group of Egyptian diabetics was found to be 35.7% and it was significantly higher than healthy volunteers (10%). Kaabia *et al* performed a cross-sectional study to determine the HCV seroprevalence in 1269 diabetic and 1315 non-diabetic patients in Tunisia; in the diabetic group, 1.3% were found to be HCV-infected compared with 0.6% in the control group ($P = 0.06$) [12].

Mehta *et al* examined the prevalence of type 2 diabetes among persons with HCV infection in a representative sample of the general adult population of the United States. They concluded that persons 40 years of age or older with HCV infection were more than three times more likely than those without HCV infection to have type 2 diabetes after adjustment for age, ethnicity, body mass index, socioeconomic status and illicit drug use [13]. The reason for this association between HCV infection and diabetes is not clear. It has been postulated that HCV could infect pancreatic islet cells and thereby directly induce damage to cells [3].

Despite lack of difference in diabetes type, diabetes duration, prevalence of hypertension, or level of glycosylated hemoglobin, diabetic patients with chronic HCV infection in this study were more likely to have macroalbuminuria than diabetic patients without HCV infection. In addition, diabetic patients with chronic HCV infection had higher mean arterial pressure, higher serum creatinine, and higher UAE. Arao and their co-workers did not find a significant difference in progression to ESRD between HCV and non-HCV diabetic patients [6].

Table 3: Comparative analysis of other risk factors for diabetic nephropathy between nephropathic patients with and without HCV infection

Patient characteristics	Nephropathy in the presence of HCV infection (n=17)	Nephropathy in the absence of HCV infection (n=12)
Diabetic duration (months), mean ± SD	100 ± 82	101 ± 77
MAP (mmHg), mean ± SD	107 ± 12	103 ± 10
Retinopathy, number (%)	6 (35.3%)	6 (50%)*
HbA1c (%), mean ± SD	8.6 ± 3.4	8.2 ± 2.9

MAP: mean arterial pressure; HA1c: glycosylated hemoglobin
* $P < 0.05$

However, the rate of progression of renal disease was reported to be worse in the HCV group [11]. Soma *et al* investigated the prevalence of HCV infection in 2370 patients who had a renal biopsy over a four-year period. The highest prevalence of HCV infection was found in type II diabetes-related glomerulosclerosis (24 of 123; 19.5%). After renal biopsy, the decline of renal function was significantly greater in the HCV-positive group than in the HCV-negative group ($P = 0.001$). In addition, they randomly examined HCV infection in 545 outpatients and inpatients with type II diabetes mellitus that did not undergo renal biopsy. Of these, 56 patients were positive for HCV antibody (10.3%), and their proteinuria was heavier than in 489 HCV-negative patients ($P = 0.001$) [14].

Poorer renal survival in HCV positive patients may be due to direct effects of HCV in the kidney [11]. Garcoa-Valdecases and his co-workers reported that HCV infection is associated with membranoproliferative glomerulonephritis and nephrotic syndrome [15]. Okada *et al* found immune complex deposition, cryoglobulin-like structure, and HCV core protein in the glomeruli of those affected patients [16]. Immune complex glomerulonephritis has been reported to occur at a higher frequency in patients with diabetic nephropathy than in the non-diabetic population [15]. Associated immune mediated glomerulonephritis in patients with diabetic nephropathy usually displays a rapid progression to renal failure [17]. There is also the possibility that HCV may infect renal tissue, such as mesangial cells, and directly contribute to renal damage [18]. In addition, it is well known that HCV infection frequently causes cirrhosis. In cirrhosis, an intense intrarenal vasoconstriction and hypoperfusion may contribute to the rapid deterioration of renal function [15].

In the present work, six out of 14 diabetic HCV-positive patients with nephropathy had diabetic retinopathy. Diabetic retinopathy is known to be present in virtually all type 1 diabetics with nephropathy, and absence of retinopathy should lead to more than usual consideration of other non-diabetic causes of renal disease [19]. On the other hand, up to one third of cases with diabetic retinopathy, even of the proliferative type, may occur in absence of renal disease or proteinuria [20].

In the absence of renal biopsy, we can only suggest the possibility of HCV infection being directly responsible for some cases of nephropathy in the present study. There are reports of renal biopsies in diabetic patients whose history was inconsistent with diabetic nephropathy (hematuria, heavy proteinuria in absence of retinopathy, or short history of diabetes) [21], and it was found that diabetic patients with HCV infection were less likely to have diabetic nephropathy as the primary renal diagnosis.

Conclusion

A high prevalence of HCV infection was observed among this group of Egyptian diabetic patients. This may have an adverse effect on the progression of nephropathy. Close monitoring is warranted for diabetics with HCV infection, with special consideration to renal and retinal complications.

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