Relationship between chronic HCV infection and diabetic microvascular complications in Egyptian patients

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Abstract: Background: Hepatitis C virus (HCV) infection and type 2 diabetes are two worldwide, major public health problems. Several studies demonstrated the link between HCV and microvascular complications of diabetes as regard progression and development while other studies fail to demonstrate that. The aim of the present study was to evaluate the effect of chronic HCV infection (Ch HCV) on the micro- vascular complications of type 2 diabetes mellitus (DM). Patients and methods: This study was conducted on 100 patients. They include 50 type 2 DM patients without chronic HCV infection (group I) and 50 type 2 DM patients with chronic HCV infection (group II) in addition to 20 healthy subjects as control group (group III). All patients were subjected to detailed history taking, clinical examination and laboratory investigations: including complete blood picture, fasting and post-prandial blood glucose and glycosylated hemoglobin (HbA1c), qualitative HCV RNA PCR test, liver profile (AST, ALT, serum bilirubin, serum albumin, INR), renal function (serum urea and creatinine, albumin/creatinine ratio (ACR). Ophthalmoscopic examinations for fundus and nerve conduction tests were done to prove retinopathy and peripheral nerve affection respectively. Results: Diabetic retinopathy was higher in diabetic patients without chronic HCV infection compared to diabetic patients with chronic HCV infection, while diabetic nephropathy and neuropathy were higher in diabetic patients with chronic HCV infection compared to diabetic patients without chronic HCV infection. Conclusions: Incidence of developing diabetic nephropathy and neuropathy was higher in diabetics with Ch HCV infection due to the double etiology, both diabetes and Ch HCV infection. On the other hand, incidence of diabetic retinopathy was lower in diabetic Ch HCV infected patients.

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1. Introduction

Hepatitis C virus (HCV) is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million persons are chronically infected with HCV and 3 to 4 million persons are newly infected each year [(1)] .

Patients with chronic hepatitis C virus (Ch HCV)infection have significantly increased prevalence of type 2 diabetes mellitus (DM) compared to controls or HBV-infected patients, independent of the presence of cirrhosis [(2)] .

It was reported that several molecules, including tumor necrosis factor alpha, suppressor of cytokine signaling 1 and 3 proteins, insulin-receptor substrates 1 and 2, and other adipocytokines, potentially are involved in the development of insulin resistance in patients with chronic hepatitis C [(3)] .

Several studies demonstrated the link between HCV and microvascular complications of diabetes (diabetic retinopathy, nephropathy and neuropathy) as regard progression and development while other studies fail to demonstrate such a link [(1)] .

The aim of this work is to study the relation between microvascular complications of diabetes mellitus and chronic hepatitis C virus infection.

2. Patients

This study is a case-control comparative study which included 100 patients with type 2 DM and 20 controls selected from the outpatients of the Internal Medicine Department of Menoufiya University Hospital in the period from June 2010 to December 2010.

The patients were classified into three groups: **Group I included** 50 type 2 DM patients without HCV infection, **Group II included** 50 type 2 DM patients with chronic HCV infection and ***Group III*** included 20 normal subjects matched for the same age as control group. An informed consent was obtained from all subjects enrolled in the study.

Exclusion criteria:

In this study we excluded patients with advanced liver or renal failure and patients with history of interferon therapy.

All patients were subjected to detailed history taking including demographic data (age, sex, duration of diabetes, family history of diabetes), clinical examination and laboratory investigations: including complete blood picture, fasting and post-prandial blood glucose and glycosylated hemoglobin (HbA1c), Qualitative HCV RNA polymerase chain reaction PCR test using the Cobas Amplicor HCV version 2.0 (Roche Diagnostics Inc., Mannheim, Germany) assay,[(4)]

liver profile (AST, ALT, serum bilirubin), serum albumin, INR) were done on autoanalyzer SYNCHRON CX5 from Beckman, renal function (serum urea and creatinine, albumin/creatinine ratio (ACR) Albuminuria was detected by Cayman's HSA EIA Kit (competitive assay) Cayman Chemical Company, Ann Arbor, Michigan 48108 USA.[5] .Nephropathy was diagnosed if there was micro or macroalbuminuria (microalbuminuria if albumin level was between 30-300 mcg per mg creatinine and macroalbuminuria if it was more than 300 mcg per mg creatinine)[6]. Ophthalmoscopic examination for fundus was done by specialist of ophthamology to prove retinopathy and nerve conduction test was done by neurologist to prove peripheral nerve affection in Menoufiya University Hospital.

Statistical methodology

Data was analyzed using Statistical Package for Social Science (SPSS) software computer program version 15. Quantitative data were presented in mean and standard deviation (SD). Qualitative data were presented in frequency and percentage. To compare between groups we used: **t-test, Chi-square test**, **ANOVA test** (analysis of variance) and LSD (least significant difference). Significance level (P) value was $P \leq 0.05$.

3. Results

There were no significant differences between the three groups as regards age, sex and body mass index. There was no significant difference between groups I and II as regards the duration of DM.

The mean systolic and diastolic blood pressure were significantly higher in group I compared to groups II & III (Table I).

There was no significant difference between the three groups as regards RBC count, WBCs count and hemoglobin concentration. The mean platelet count was significantly lower in group II compared to groups I & III.

The mean fasting blood sugar, 2 hours post-prandial blood sugar and HbA1C were significantly higher in groups I and II compared to group III (Table III) .

The mean ALT, AST, serum bilirubin and INR were significantly higher in group II compared to groups I & III. The mean serum albumin level was significantly lower in group II compared to groups I & III.

The mean serum creatinine was significantly higher in groups I and II compared to group III. There was no significant difference between the three groups as regards mean blood urea.

Diabetic nephropathy was present in 12 (24%) patients of group I and 22 (44%) patients of group II, it was significantly higher in group II. Diabetic neuropathy was present in 14 (28%) patients of group I and 24 (48%) patients of group II, it was significantly higher in group II. Diabetic retinopathy was present in 18 (36%) patients of group I and 9 (18%) patients of group II, it was significantly lower in group II,

The mean age, mean duration of DM, HBA1C, systolic and diastolic blood pressure were significantly higher in nephropathy +ve patients compared to nephropathy –ve patients in both groups I & II.

In groups I & II, the mean age, mean of duration of DM and HBA1C were significantly higher in neuropathy +ve patients compared to neuropathy –ve patients.

In groups I & II, the mean age, mean of duration of DM and HBA1C were significantly higher in retinopathy +ve patients compared to retinopathy –ve patients.

Table I: Comparison between the three groups as regards blood pressure

	Group I (n= 50)	Group II (n= 50)	Group III (n= 20)	ANOVA test	LSD
Systolic blood pressure (mmHg)					
Mean ± SD	143.8± 22.57	122± 14.28	126 ± 17.88	P < 0.001*	GI vs GII & GIII
Diastolic blood pressure (mmHg)					
Mean ± SD	90.9 ± 9.51	70.0 ± 7.62	80.0 ± 9.98	P < 0.001*	GI vs GII & GIII

Table II: Comparison between the three groups as regards platelet count

	Group I (n= 50)	Group II (n= 50)	Group III (n= 20)	ANOVA test	LSD
Platelet count ($x10^3$/cc)					GI1vs GI & GIII
Mean ± SD	253.1±57.38	172.2 ± 52.6	254.1± 45.33	P< 0.001*	

Table III: Comparison between the 3 groups as regards blood glucose profile

	Group I (n= 50)	Group II (n= 50)	Group III (n= 20)	ANOVA test	LSD
FBS (mg/dl)					
Mean ± SD	146.04 ± 22.41	140.68 ± 32.88	81.35 ± 6.83	P < 0.001*	GI1vs GI & GIII
PPBS (mg/dl)					
Mean ± SD	211.90 ± 45.5	204.40 ± 42.33	101.4 ± 5.09	P < 0.001*	GI1vs GI & GIII
HBA1C (%)					
Mean ± SD	8.30 ± 1.27	8.37 ± 1.41	5.11 ± 0.39	P < 0.001*	GI1vs GI & GIII

Table IV: Comparison between group I and group II as regards incidence of micro-vascular complication

		Group I (n = 50)	Group II (n = 50)	X^2-test
Nephropathy	+ve	12 (24%)	22 (44%)	P = 0.035*
	-ve	38 (76%)	28 (56%)	
Neuropathy	+ve	14 (28%)	24 (48%)	P = 0.039*
	-ve	36 (72%)	26 (52%)	
Retinopathy	+ve	18 (36%)	9 (18%)	P = 0.042*
	-ve	32 (64%)	41 (82%)	

Table V: Comparison between nephropathy +ve and –ve patients in group I and group II as regard age, duration of DM, glycated hemoglobin level, blood pressure

Group I		**Nephropathy +ve (n = 12)**	**Nephropathy –ve (n = 38)**	**t-test**
Age (years)	Mean± SD	50.28 ± 8.9	43.11 ± 8.2	P = 0.009*
Duration of DM (years)	Mean± SD	16.71 ± 7.9	11.44 ± 7.3	P = 0.031*
HbA1C (%)	Mean± SD	9.04 ± 1.6	8.03 ± 1.0	P = 0.010*
Systolic BP (mmHg)	Mean± SD	159.29 ± 24.6	134.17 ± 21.7	P <0.001*
Diastolic BP (mmHg)	Mean± SD	92.68 ± 11.4	85.56 ± 10.6	P =0.037*
Group II		**Nephropathy +ve (n = 22)**	**Nephropathy –ve (n = 28)**	**t-test**
Age (years)	Mean± SD	51.00 ± 6.7	40.77 ± 6.8	P < 0.001*
Duration of DM (years)	Mean± SD	19.00 ± 6.0	8.25 ± 5.5	P < 0.001*
HbA1C (%)	Mean± SD	9.27 ± 1.7	7.86 ± 0.89	P < 0.001*
Systolic BP (mmHg)	Mean± SD	150.59 ± 17.8	121.5 ± 15.0	P<0.001*
Diastolic BP (mmHg)	Mean± SD	94.06 ± 8.7	76.97 ± 9.5	P <0.001*

Table VI: Comparison between neuoropathy +ve and –ve patient in group I and group II as regard age, duration of DM, glycated heamoglobin level, blood pressure

Group I		**Neuropathy +ve (n = 14)**	**Neuropathy –ve (n = 36)**	**t-test**
Age (years)	Mean± SD	56.0 ± 4.7	42.6 ± 7.4	P < 0.001*
Duration of DM (years)	Mean± SD	22.5 ± 4.2	10.57 ± 6.5	P < 0.001*
HBA1C (%)	Mean± SD	10.0 ± 1.4	7.88 ± 0.8	P < 0.001*
Systolic BP (mmHg)	Mean± SD	143.0 ± 31.3	133.85 ± 35.4	P =0.895
Diastolic BP (mmHg)	Mean± SD	89.0 ± 11.0	86.5 ± 10.3	P = 0.511
Group II		**Neuropathy +ve (n = 24)**	**Neuropathy –ve (n = 26)**	**t-test**
Age (years)	Mean± SD	54.00 ± 4.2	41.62 ± 6.05	P < 0.001*
Duration of DM (years)	Mean± SD	21.07 ± 4.5	8.91 ± 5.8	P < 0.001*
HBA1C (%)	Mean± SD	9.79 ± 1.8	7.87 ± 0.8	P < 0.001*
Systolic BP (mmHg)	Mean± SD	126.92 ± 20.2	132.97 ± 21.5	P =0.303
Diastolic BP (mmHg)	Mean± SD	77.69 ± 11.7	84.32 ± 11.9	P = 0.084

Table VII: Comparison between retinopathy +ve and –ve patient in group I and group II as regard age, sex duration of DM glycated heamoglobin level, blood pressure and duration of HCV infection

Group I		**Retinopathy +ve (n = 18)**	**Retinopathy –ve (n = 32)**	**t-test**
Age (years)	Mean± SD	50.7 ± 7.8	41.36 ± 6.9	P < 0.001*
Duration of DM (years)	Mean± SD	19.52 ± 5.6	9.57 ± 6.5	P < 0.001*
HBA1C (%)	Mean± SD	9.35 ± 1.6	7.74 ± 0.5	P < 0.001*
Systolic BP (mmHg)	Mean± SD	155.9 ± 25.3	133.6 ± 21.6	P =0.004*
Diastolic BP (mmHg)	Mean± SD	93.8 ± 11.7	84.7 ± 9.6	P =0.014*
Group II		**Retinopathy +ve (n = 9)**	**Retinopathy –ve (n = 41)**	**t-test**
Age (years)	Mean± SD	52.92 ± 4.9	41.66 ± 6.3	P < 0.001*
Duration of DM (years)	Mean± SD	20.07 ± 5.3	9.0 ± 6.1	P < 0.001*
HBA1C (%)	Mean± SD	9.87 ± 1.7	7.86 ± 0.8	P < 0.001*
Systolic BP (mmHg)	Mean± SD	147.86 ± 20.8	124.4 ± 17.8	P <0.001*
Diastolic BP (mmHg)	Mean± SD	89.3 ± 11.4	80.28 ± 11.1	P =0.014*

4. Discussion

Hepatitis C virus (HCV) infection and type 2 diabetes mellitus (DM) are two worldwide, major public health problems with increasing complications and mortality rates. Egypt contains the highest prevalence of hepatitis C in the world [7]

The classic view of metabolic and hemodynamic alterations as the main causes of microvascular injury in diabetes has been transformed significantly, with clear evidence indicating that these traditional factors are only a partial aspect of a much more complex picture. One of the most important changes is related to the participation of immune-mediated inflammatory processes in the pathophysiology of diabetes mellitus and its complications [7].

The current study found that nephropathy was higher in Ch HCV-DM patients (44%) compared to T2DM patients (24%). This agrees with **Sahar *et al.,*** [8] and **Soma *et al.,*** [9]. On contrary, **Kuriyama *et al.,*** [10] found that nephropathy was lower in Ch HCV-DM (10%) compared to T2DM (17%). In this study it was observed that the incidence of nephropathy was lower in Ch HCV-DM patients compared to our study which can be explained by better glycemic control observed in **Kuriyama *et al.,*** [10] study (HbA1C 6.8 %) compared to our study (8.3 %) also shorter duration of DM (8) years in T2DM patients and (5) years in Ch HCV-DM compared to (13.1 and 11.6) years in our study.

Hepatitis C virus (HCV) is known to have direct effects in the kidney, such as membranous nephropathy, cryoglobulinemia, and membrano-proliferative glomerulonephritis (MPGN). The presence of HCV worsens the progression of several renal diseases, and contributes to the excess of renal disease, and this effect may have a relatively greater impact among diabetic patients [11]. It was found that HCV is associated with increased risk for end stage renal disease (ESRD) among patients with DM. HCV has been reported to cause glomerular disease, increase the risk of albuminuria, and accelerate progression of diabetic nephropathy additionally [12,13] .

In study by **Errol *et al.,*** [14], HCV was a significant predictor of reaching ESRD independent of initial renal function, proteinuria, blood pressure, sex, race, presence of diabetic nephropathy, age, or duration of diabetes. Poorer renal survival in the HCV patients may be due to direct effects of HCV in the kidney. Baseline viral load is an independent positive predictor for chronic kidney disease [13] .

The mechanism of HCV-related renal disease is uncertain, research suggests that glomerular injury results from deposition of circulating immune complexes that contain hepatitis C antibodies, antigens, and complement [12]. Other study has shown that inflammatory cytokines, are determinant in the development of micro-vascular diabetic complications [15]. Diabetic patients with nephropathy have higher serum concentrations of tumor necrosis factor alpha (TNF-α) than non-diabetic subjects or diabetic patients without renal involvement, with a significant rise in serum TNF-α as diabetic nephropathy progresses [16,17]. TNF- is cytotoxic to glomerular, mesangial, and epithelial cells, and may induce direct renal damage. Moreover, TNF- has a direct effect on the protein permeability barrier of the glomerulus independent of alterations in hemodynamic factors or effects of recruited inflammatory cells [18].

Peripheral neuropathy (PN) in our study was found higher in Ch HCV-DM patients (48%) compared to T2DM patients (28%). **Sahar *et al.,*** [8] found that PN was higher in Ch HCV-DM (33.5%) compared to T2DM (24%). **Kuriyama *et al.,*** [10] found that PN was lower in Ch HCV-DM (20%) compared to T2DM (35%).

In study made by **Zaltron *et al.*,**[19] PN was found to be present in 23/68 patients with hepatitis C and detectable cryglobulins (CG).

PN is described in 9% of patients chronically infected by HCV and when cryoglobulinemia is present this number can rise to more than 30%.[20-22] Although PN in HCV has greater association with increased CG, several papers have described it in the absence of CG.[23-25] Recently, after finding the virus RNA in nerve biopsies, some authors suggested a direct viral aggression against the nerve[26] . However, PN seems to the result from immunomediated mechanisms determined by the HCV in the nerve rather than related to direct viral infection with consequent *in situ* lesion in the nervous tissue[27] .

PN associated with HCV is usually related to axonal damage, probably secondary to vasculitis, fascicular ischemia and subsequent axonal degeneration [28]. Usually the peripheral nervous system involvement is described as a sensory-motor, distal polyneuropathy often with cryoglobulinemia[29], but isolated mononeuropathy, such as carpal tunnel syndrome or multiple mononeuropathy seem common[30] .

PN is the most common complication of mixed cryoglobulinemia and result of axonal ischemic damage. Two main pathogenic mechanisms have been suggested, represented by deposits of CG in the vasanervrum microcirculation and vasculitis [31]. Recently a role of anti neuronal antibodies has been suggested[32].

Moreover, it was demonstrated that HCV core protein activates human glia and contributes to neurotoxicity. Direct exposure of HCV core protein to primary human neurons suppressed the neuronal autophagy, leading to neurite retraction. The change in neuronal membrane potential after exposure to HCV core protein indicated that core was biologically active at the cell membrane and was able to modulate ionic conductance in neurons. In addition to direct neurotoxicity, proinflammatory cytokines and other neurotoxins released from HCV core-activated microglia into supernatants were toxic to neurons[33] .

Retinopathy in our study was found higher in T2DM patients (36%) compared to Ch HCV-DM patients (18%).

The low prevalence of diabetic retinopathy in diabetic patients with hepatitis C chronic liver diseases may be related to liver disease induced abnormalities protecting the cardiovascular system from atherosclerosis (hypotension, coagulation defect and decreased platelet count)[34] .

In our study we observe that Ch HCV-DM patients had significantly lower mean systolic and diastolic blood pressure compared to T2DM. Also we observe significant decrease in platelet count and significant increase in INR in Ch HCV-DM compared to T2DM and control. These effects of Ch HCV infection may decrease diabetes induced hypercoagulation and premature atherosclerosis induced by factors including, increased Levels of platelet-derived micro particles (MPs) and monocyte-derived MPs[35] .

Increase mean platelet volume (a marker associated with platelet reactivity) has been demonstrated to be increased in diabetes particularly associated with diabetic retinopathy[35].

A lower activity of the system anti thrombin III-heparin, a higher activity of fibrinogen and activation of the fibrinolytic system were observed in diabetic patients with retinopathy (micro-angiopathy) compared to diabetics without retinopathy [36] . More than this chronic liver diseases (CLD) including Ch HCV infection have low serum level of lipids especially low serum lipoprotein LP(a) which competes with plasminogen for bending to fibrin impairing fibrinolysis. High LP (a) is associated with the development and progression of retinopathy in diabetic patients and there is correlation between the severity of diabetic retinopathy and LP(a)[37] .

Sahar *et al.*, [8] found that retinopathy was lower in Ch HCV-DM (29%) compared to T2DM (51%), **Kuriyama *et al.*,**[10] found that retinopathy was lower in Ch HCV-DM (20%) compared to T2DM (39%) and **Fujiwara *et al.*,** [38] found that retinopathy was higher in T2DM (53%) compared to LC-DM (16%), while, **Soma *et al.*,** [9] found that retinopathy was comparable in the two groups (47%) in Ch HCV-DM and (44.55) in T2DM.

Proliferative diabetic retinopathy is characterized by an early pathological micro-vascular obstruction and retinal ischemia. Platelet adhesion seems to be more important in pathogenesis of retinopathy (micro vascular occlusion, neovascularization and progression of retinopathy) than in other diabetic micro-vascular complications[39]. Unlike nephropathy and neuropathy, diabetic retinopathy is not known to be one of extrahepatic manifestations of HCV and this may give the chance for the protective effects of HCV CLD to take the upper hand making retinopathy lower in Ch HCV-DM compared to T2DM[37] .

This study clarified that several factors might affect the occurrence of diabetic micro vascular complications including longer duration of diabetes, high HbA1c, high blood pressure and longer age were observed in patients with diabetic triopathy as compared to those without triopathy.

Skyler *et al.*, [40] found that chronic hyperglycemia , duration of DM and hypertension are prominent risk factors for diabetic-angiopathy. **Rani *et al*.**, [41] found that the duration of diabetes, however, remained the strongest predictor for any diabetic retinopathy and its severity. Longer duration of diabetes, lean BMI, hyperglycemia coupled with other risk factors. Male gender was

observed to be associated with the presence of any diabetic retinopathy, but not its severity.

Conclusion

Incidence of developing diabetic nephropathy and neuropathy was higher in diabetics with Ch HCV infection due to the double etiology, both diabetes and Ch HCV infection . CH HCV can on its own produce nephropathy and peripheral neuropathy as extrahepatic manifestation. Incidence of diabetic retinopathy was lower in diabetic Ch HCV infected patients could be explained that retinopathy is not known to be one of extrahepatic manifestations of HCV. Platelet adhesion seems to be more important in pathogenesis of retinopathy (micro vascular occlusion, neovascularization and progression of retinopathy) than in other diabetic micro-vascular complications. This may give the chance for the protective effects of CLD (through Ch HCV induced thrombocytopenia, low coagulation functions) to take the upper hand making retinopathy lower in Ch HCV-DM compared to T2DM. Duration of diabetes, age, glycemic control and blood pressure are prominent risk factors for diabetic micro-angiopathy. Strict control of blood glucose, therefore, should be directed in patients with diabetic Ch HCV to help in preventing diabetic angiopathy in those patients. Further study is needed to find the relevance between diabetic angiopathy and insulin resistance in CLD patients.

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