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Association of Diabetes with Hepatitis C. Virus (HCV) Infected Male and Female Patients Along with Different Risk Factors

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ABSTRACT

Presently in Pakistan the rates of HCV caused infection is about 8 - 10% in general population, where as diabetes prevalence is in 12% of people above 25 years of age. The associated risk factors in HCV and diabetes are very common in Pakistan. This study was conducted to prove association between diabetes, hepatitis C and different risk factors bio-chemically and epidemiologically, establish potential relationship (s) and determine independent associations of covariates with diabetes and HCV infection abnormalities. A total of 700 consecutive patients were prospectively selected. On the bases of recorded data, patients were classified as having HCV positive (without diabetes) N = 532 (76%), HCV positive with diabetes N = 118 (16.85%) and normal N = 50 (7.14%) as control. Data showed that HCV infection was independently related to glucose abnormalities and there was a three folds increase in the prevalence of diabetes in HCV subjects. Our study provided evidence that there is a definite relation between HCV infection and diabetes and both were more common in females than males. Married individuals were more susceptible to HCV and diabetes than unmarried. Risk factors have been also associated with HCV infection and diabetes.

Key Words: HCV; Diabetes; Heart disease; Liver function tests; Lipid profiles; Nephrpahy

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, affecting 3% of the world's population. HCV prevalence in adults between 40 and 74 years of age in Pakistan has arisen to 8 - 10% (Batool & Qureshi, 2006). The disease is characterized by silent onset in most infected individuals and recent studies indicate that the rate of progression to advanced liver disease might be lower than previously assumed (Seeff *et al.,* 2000). HCV mainly affects the liver, but also several other tissues outside the liver have been reported to be involved, resulting in a wide spectrum of extrahepatic manifestations. The burden of disease associated with HCV infection is likely to increase during the next 10 - 20 years (Salomon *et al*., 2002). The prevalence of type 2 diabetes in people living in the developed world ranges from 2.0 to 9.4% (King *et al*., 1998). Diabetes prevalence in Pakistan has arisen to 12% in adults (Fatema, 2003). The decline in mortality of people with diabetes, together with the rapidly increasing frequency of obesity and the sedentary lifestyle of the population, portends a dramatic increase in prevalence (Wild *et al*., 2004). Therefore both HCV liver disease and diabetes, already prevalent diseases, are likely increase in the next decades (Nocente *et al*., 2003).

During the last decade, it was hypothesized that diabetes could be one more extrahepatic condition attributable to HCV infection. This raises the intriguing question of whether the rise in HCV infection is contributing to the increasing prevalence of diabetes. An increased prevalence of diabetes and impaired glucose tolerance has been consistently found in liver cirrhosis from any cause (Thuluvath & John, 2003). Several reports have claimed a specific association between HCV infection and type-2 diabetes, but in most instances patients were a mixture of cases with cirrhosis, hepatitis and diabetes (Wilson *et al*., 2004).

Hepatitis C is known to have a wide variety of manifestations in the kidney. The renal manifestations of HCV include direct effects in the kidney, such as membranous nephropathy, cryoglobulinemia, and membranoproliferative glomerulonephritis (MPGN) (Gopalani & Ahuja, 2001). The presence of HCV worsens the progression of several renal diseases (Sulkowski & Thomas, 2003). HCV has been reported to have high prevalence of diabetic patients with diabetic nephropathy. Its infection may reach an incidence of 50% in patients with end-stage renal disease (Gentil *et al*., 1999). Therefore it is plausible that HCV contributes to the excess of renal disease seen in the patients and this effect may have a relatively greater impact among diabetic patients and it has also been identified as an independent risk factor for predicting the development of post transplant diabetes mellitus (PTDM) (Yildiz *et al*., 2002). These evidences reinforce the hypothesis that HCV is the cause rather than the consequence of diabetes. In addition, the link between HCV

and diabetes may contribute substantially to the detrimental role of HCV on patient and graft survival after liver and/or renal transplantation (Abbott *et al*., 2004). The diabetes management requires equal attention to control of blood glucose, cholesterol, blood pressure and other cardiovascular risk factors, because out of three people with diabetes one die from heart disease and stroke (The American Diabetes Association's 64th Annual Scientific Sessions, 2005). The objective of the present study was directed towards clinical and epidemiological investigations and association between HCV infection and diabetes. In addition, the physiopathological mechanisms related to the association between HCV and diabetes is also discussed. In this study, we also examine the effects of HCV on different risk factors in patients with diabetes and hepatitis C disease.

MATERIALS AND METHODS

A total of 700 patients attending the outpatient unit of District General Hospital, Military Hospital and Al-Noor Laboratories at Rawalpindi were recruited from June 2003 to January 2005. Anti-HCV^+ patients were referred from two main sources: from the blood bank of hospitals and from general practitioners. On the basis of samples collected the patients were divided into three groups according to their HCV antibody status: anti-HCV^+ without Diabetes (n = 532) and anti-HCV^+ + Diabetes (n = 118) patients and normal (control n = 50). The demographic data was obtained by interviewing the patients at the time of sampling. The patients were analyzed for the variables such as age, sex, martial status, weight, obesity, type of diabetes, disease duration, disease treatment, previous hospital admission, economic status, hypertension, nephropathy, retinopathy, neuropathy and blood transfusion and other complications arising from HCV and diabetes. Plasma fractions were collected in tubes and liver function tests. Blood glucose (randam & fasting) and lipid profiles were performed by using microlab 300 l x Merck where as serological testing for anti-HCV was done using a second-generation commercial enzyme immunoassay (Abbot Laboratories, Chicago, IL) according to the manufacturer's instructions. For patients, not previously diagnosed for diabetes, the criteria recommended by the Expert Committee on the Diagnosis and Classification of Diabetes were used that stated that diabetes was diagnosed if the fasting blood glucose was $\geq$ 7 mmol, or (120 mg/dL). Based on the clinical information, all diabetic patients in this study had type-2 diabetes. Informed written consent was obtained from all participants. Patients were categorized as chronic hepatitis C with diabetes, diabetes without HCV infection and control having no symptoms of disease separately. For statistical procedure and calculations data was analyzed by applying Spearsman correlation and chi square test using SPSS ver. 10 for windows. The values were expressed as mean ± SE.

RESULTS

Out of a total of 700 patients samples, 532 (76%) were HCV positive of which 192 (36.1%) were male and 340 (63.9%) were females and 499 (93.8%) patients were married, while 33 (6.2%) were un-married. From married individuals 182 (34.2%) were males and 317 (59.6%) females, while from un-married patients 10 (1.9%) were males and 23 (4.3%) females. It was also observed that 218 subjects (41.0%) of the samples collected fell between 40 to 60 years age group and 298 (56.5%) of total collected samples show weight between 55 - 74 kg (Table I).

In the present study 192 (36.1%) HCV infected males and 340 (63.9%) HCV infected females patients from 532 samples were taken into consideration (Table II). The alanine aminotransferase (ALT) and alkaline phosphate (ALP) value obtained from the data from HCV patients were further analyzed on the basis of marital status, which yielded significant correlation ($r = 0.291$; $P < 0.001$ for ALT and $r = 0.255$; $P < 0.002$ for ALP). Likewise, the values obtained in case of blirubin had a significant correlation with hepatitis infection ($r = 0.236$; $P < 0.001$). The total serum protein and albumin were highly significant ($P < .0001$) but negatively associated to each other ($r = - 0.218$).

Heart disease was found only in five (71.64%) married and two (28.36 %) un-married male patients, whereas total of 19 (55.88%) married and 15 (45.22%) un-married patients were at high risk for heart disease. In females (340) on further study for married and un-married subjects it was found that heart disease was found only in two (66.66%) married and one (33.34%) un-married patients, whereas 14 (65.12%) married and six (34.88%) un-married patients were at high risk for heart disease. The lipid profile levels were found to be very high in these individuals (Table II). These results showed a weak association between HCV and lipid profiles ($r = 0.199$). This revealed that for un-married the percentages of heart patients and risk patient were 20% and 10.43%, respectively. On the other hand, 118 Samples were hepatitis-C infected and also diabetic out of which 44 were male and 74 (37.28%) females and 62.71% of total subjects. From these patients 89.83% were married, while 10.16% un-married. Out of these 106 married individuals 36.44% were male and 53.38% female, while from 10.16% un-married patients 0.8% were male and 9.32% female. It was also note that 43.0% subjects fell between 40 - 60 age group and 54.5% patients had weight between 55 - 74 kg. A total of 118 (18.28%) male and female (married/un-married) patients were with increased random blood glucose levels, indicating that the patients with HCV infection were also suffering from diabetes. These patients were than categorized into type-1 insulin dependent diabetes mellitus (IDDM) and type-2 non-insulin dependent diabetes mellitus (NIDDM) diabetes. It was noted that only 28.82% patients were suffering from type-1 diabetes. Out of these patients 32.36% were male and 67.64% females. Type-2 diabetes was found in 71.18% patients out of which 39.3% were

Table I. Weight, age, martial status and sex cross tabulation

Weight Group	Martial status	Age Group	Gender		Total
			Male	Female	
35-54	Married	16-30	0	5	5
		31-45	2	14	
		46-60	5	27	32
		61-75	5	14	19
		76 and Above	2	0	2
		Total	14	60	74
	Single	16-30	1	6	7
		61-75	0	1	1
		Total	1	7	8
55-74	Married	16-30	8	13	21
					106
		46-60	45	122	167
		61-75	47	59	106
		76 and Above	9	6	15
		Total	109	200	309
	Single	16-30	2	5	7
		31-45	0	8	8
		46-60	1	5	6
		61-75	3	1	4
		76 and Above	3	8	11
		Total	9	27	36
75-94	Married	16-30	10	3	13
		31-45	50	31	81
		46-60	43	63	106
		61-75	26	18	44
		76 and Above	0	6	6
		Total	129	121	250
	Single	16-30	2	1	3
		31-45	6	2	8
		46-60	0	1	1
		61-75	1	0	1
		Total	9	4	13
95-114	Married	16-30	0	5	5
		31-45	7	9	16
		46-60	7	25	32
		61-75	0	6	6
		76 and Above	0	2	2
		Total	14	47	61
	Single	16-30	1	0	1
		31-45	3	0	3
		76 and Above	0	1	1
		Total	4	1	5
115 and Above	Married	31-45	3	0	3
		46-60	2	4	6
		61-75	2	0	2
		Total	7	4	11
	Single	16-30		2	2
		Total		2	2

male and 60.7% females. It was observed that 90.67% patients were married and 9.33% un-married. From these 90.67% married individuals 36.4% were male and 54.2% female, whereas 0.8% were male and 8.5% female un-married patients.

In the present study analysis of 118 samples form HCV infected patients with diabetes indicated that 48.30% diabetic patients had family history, while 52.70% patients had no family history. This showed that 48.30% subjects were genetically susceptible to acquire diabetes. In this category, majority of the subjects were diagnosed to have diabetes between 35 - 60 years of age. From the study, it became clear that subjects having no family history of diabetes might develop diabetes due to HCV infection in the age of 46 - 60 years.

In all 118 cases of known HCV infection with diabetes, heart disease was also found in 21.18% patients of total 118 subjects whereas 38.13% patients were at high risk for heart disease. Furthermore the lipid profile levels were found to be high in these individuals (Table III). Heart disease was found only in 11.51% married and 36.36% un-married patients, whereas 44.44% married and 37.32% un-married patients were at high risk of this disease. Data showed a strong correlation (r = 0.246) between HCV and diabetes and heart disease, which indicated increased chances of having heart disease in HCV patients with diabetes. Different epidemiological risk factors contributing to the development of HCV infection showed that 15.22% patients from the group of 532 patients and 34 (28.8%) from the group of 118 patients were obese having body mass index (BMI) > 40 compared to normal BMI = 20 - 25. Further it was observed that 37.7% out of 532 and 56.7% patients out of 118 were at risk of obesity due to their slightly high BMI 25 - 30. It was observed that 40.9% and 33.8% patients were under socioeconomic stress, earning was below Rs 5000 per month, which was taken as economic stress point.

Previous studies have shown that many diseases are associated with HCV infection (Bacon *et al.,* 2002). Therefore during this study, nephropathy disorders were seen in 6.43% and 49.29% patients, where as 12.81% and 39.31% showed retinopathy disorders. It was noted that neuropathy problems were present in 07.70% and 27.89% patients. Hypertension is another risk factor for patients suffering from HCV infection. Therefore it was noted that out of 532 subjects 48.1% and out of 118 subjects 50.5% patients were hypertensive as their blood pressure was > 120/80 Hg. Urinary track infections were also seen in 23.8% and 48.47% patients. The history of the patients revealed that 14.11% and 13.55% patients had taken blood transfusion, 20.6% and 7.6% patients had been hospitalized and 30.39% and 22.9% patients had gone through surgical process each at least once in their life; 15.8% and 21.2% patients often visited to barber. It was studied that 3.8% and 1.7% patients were suffering from tuberculosis where as 39.66% and 9.34% patients were found to be habitual for taking injections out of 532 and 118, respectively.

DISCUSSION

During this study we have seen a tight correlation between HCV and diabetes. Lecube *et al*. (2004) earlier reported that there are chances of HCV patients to get diabetes. The higher prevalence of HCV in our study parallels the higher prevalence and incidence rates of diabetes. One possible reason why HCV was associated with higher prevalence of diabetes is that as both NIDDM and HCV chronic infection are closely linked to steatosis, which is supposed to be a mediator of insulin resistance in

Table II. Clinical variables considered in patients having HCV Infection. N = 532

Clinical Parameters	532 HCV Positive Subjects							
Parameters	**Male**		**Female**		**Mean Values Obtained**	**P values**	**R Values**	**Normal Values**
	Married	**Un-married**	**Married**	**Un-married**				
Subjects	**182**	**10**	**317**	**23**	**532**	**532**	**532**	
Alanine Aminotransferase ALT (U L^{-1})	115.76 ± 3.09	112.20 ± 9.84	113.26 ± 2.51	129.22 ± 11.80	114.79 ± 1.91	0.001**	0.301	9-43
Aspartate Aminotrans-ferase AST (U L^{-1})	104.74 ± 2.67	89.95 ± 8.50	104.30 ± 3.93	118.43 ± 10.58	104.79 ± 2.56	0.001**	0.291	10-35
Alkaline Phosphatase ALP (U L^{-1})	431.31 ± 7.55	408 ± 13.58	434.18 ± 5.60	473.22 ± 27.30	434.79 ± 4.39	0.002*	0.255	< 258
Bilirubin (mg dL^{-1})	3.71 ± 0.14	3.75 ± 0.32	4.01 ± 0.11	3.46 ± 0.39	03.87 ± 0.08	0.001**	0.236	≤ 0.2
Total Protein (g dL^{-1})	7.70 ± 0.07	7.45 ± 0.47	7.69 ± 0.05	7.23 ± 0.17	07.68 ± 0.04	0.001**	- 0.218	6-7
Albumin (g dL^{-1})	37.87 ± 0.21	40.80 ± 1.99	38.13 ± 0.36	38.65 ± 1.11	37.97 ± 0.27	0.001**	-0.243	44-48
Cholesterol (mg dL^{-1})	293.34 ± 1.55	290.31 ± 1.45	294.34 ± 1.57	293.31 ± 1.48	294.91 ± 1.31	0.001**	0.246	≤ 200
Triglycride (mg dL^{-1})	288.72 ± 1.69	287.73 ± 1.69	298.72 ± 1.60	277.74 ± 1.72	278.72 ± 1.93	0.002*	0.211	140-200
High density lipoproteins HDL (mg dL^{-1})	36.22 ± 1.33	34.29 ± 1.35	34.22 ± 1.33	33.29 ± 1.65	37.81 ± 1.36	0.001**	-0.173	> 60
Low density lipoproteins LDL (mg dL^{-1})	183.61 ± 1.56	186.71 ± 1.56	188.23 ± 1.96	184.61 ± 1.56	196.61 ± 1.54	0.003*	-0.199	< 100
Random blood glucose (mg dL^{-1})	173.87 ± 1.93	174.20 ± 10.38	172.88 ± 1.82	160.22 ± 6.83	172.07 ± 1.32	0.067	0.111	125-155
Fasting blood glucose (mg dL^{-1})	91.99 ± 1.06	95.60 ± 3.77	92.31 ± 0.85	85.78 ± 1.32	91.98 ± 0.64	0.077	0.103	65-99

**Highly significant *Significant

Table III. Clinical variables considered in patients having HCV Infection along with diabetes. N = 118

Clinical Parameters	118 HCV Positive Subjects							
Parameters	**Male**		**Female**		**Mean Values Obtained**	**P values**	**R Values**	**Normal Values**
	Married	**Un-married**	**Married**	**Un-married**				
Subjects (n)	**43**	**01**	**63**	**74**	**118**	**118**	**118**	
Alanine Aminotransferase ALT (U L^{-1})	131.28 ± 5.01	122.20	133.27 ± 2.59	129.27 ± 9.80	131.28 ± 5.01	.001**	0.299	9-43
Aspartate Aminotrans-ferase AST (U L^{-1})	118.00 ± 4.77	109.30	122.30 ± 5.93	118.45 ± 09.58	118 ± 4.77	0.001**	0.311	10-35
Alkaline Phosphatase ALP (U L^{-1})	419.36 ± 7.52	438	431.18 ± 5.11	463.42 ± 17.30	419.36 ± 7.52	.001**	0.289	< 258
Bilirubin (mg dL^{-1})	4.26 ± 0.21	5.55	4.81 ± 0.11	3.40 ± 0.38	04.26 ± 0.21	0.001**	0.271	≤ 0.2
Total Protein (g dL^{-1})	8.73 ± 1.07	7.66	8.43 ± 0.63	7.13 ± 0.78	07.81 ± 0.08	.001**	- 0.201	6-7
Albumin (g dL^{-1})	37.87 ± 1.21	33.85	37.14 ± 0.96	32.15 ± 1.01	38.64 ± 0.55	.001**	-0.239	44-48
Cholesterol (mg dL^{-1})	298.88 ± 6.46	278.31	293 ± 5.11	299 ± 4.32	278.88 ± 6.46	.001**	0.319	≤ 200
Triglycride (mg dL^{-1})	317.80 ± 5.87	290.51	293 ± 7.21	279 ± 5.32	257.80 ± 5.87	.001**	0.346	140-200
High density lipoproteins HDL (mg dL^{-1})	41.85 ± 2.56	48.31	39 ± 2.09	33.76 ± 2.32	41.85 ± 2.56	0.001**	-0.235	> 60
Low density lipoproteins LDL (mg dL^{-1})	236.97 ± 5.69	248.72	233 ± 5.99	269 ± 4.51	236.97 ± 5.69	.001**	-0.217	< 100
Random blood glucose (mg dL^{-1})	298.05 ± 2.55	296	299.77 ± 8.39	290 ± 1.89	298.05 ± 2.55	0.001**	0.397	125-155
Fasting blood glucose (mg dL^{-1})	214.27 ± 2.41	211.17	221.13 ± 5.57	213.21 ± 3.91	214.27 ± 2.41	0.001**	r = 0.388	65-99

HCV-positive subjects. Presently, it is un-known what makes an individual susceptible to the development of diabetes after a viral infection. A genetic susceptibility for the development of diabetes type-1 has been well documented in some individuals. Whatever the triggering mechanism (s) for the development of diabetes in susceptible individuals, DM1 or insulin dependent diabetes has been associated with genetic markers known as human hystocompatibility antigens (HLA). Resistance to the development of diabetes has also been associated with HLA antigens. Un-fortunately, we do not have sufficient data to comment on the state of liver disease in HCV patients, although heart disease was also found in both groups. These results are in accordance with those of Matsumori (2005) who found a high prevalence of HCV infected patients with hypertrophic cardiomyopathy, dilated cardiomyopathy and myocarditis. In this context Omura *et al.* (2005) noted that transgenic mice for the HCV-core gene develop ventricular dilatation, cardiac dysfunction and myocardial fibrosis at 12 months, similar to the pathological manifestations observed in human dilated cardiomyopathy. Furthermore, it has been pointed out by Omura *et al.* (2005) that although HCV infection may be the cause of several phenotypically different cardiomyopathies, mild inflammation with mononuclear cell infiltration have also been observed with HCV infection in humans.

During this study we found that 20.27% diabetic patients with HCV had worse renal survival and these effects of HCV were independent of other factors shown to affect renal survival (Table I & II). Similar effect of HCV was observed by Soma *et al*. (2000) in a retrospective study of patients with chronic kidney disease (CKD). In their study, the prevalence of HCV was highest (19.5%) in patients with diabetes who had a renal biopsy. Of interest, renal biopsies were done in patients with diabetes, because the history was inconsistent with diabetic nephropathy (hematuria, heavy proteinuria in absence of retinopathy, or short history of diabetes). Likewise, diabetic patients with HCV had three times greater diabetic nephropathy as their primary diagnosis. Similarly, the rate of progression of renal disease was worse in the HCV group with diabetes. In our study, renal function was poor in HCV with diabetes than HCV group, with the majority of patients showing higher CKD. Therefore, the entire cohort was at significant risk of renal disease progression.

The HCV patients differed from non-HCV patients in only a few areas. Among these, blood pressure would be most likely to affect renal survival. However, the effects of HCV on renal survival were independent of both initial and follow-up blood pressure. It is interesting that low-density

lipoprotein (LDL) and total cholesterol were significantly lower in majority of the subjects from HCV group (Table III). It is, however, not clear why this is the case, but it may represent an increased state of inflammation or altered caloric metabolism. Notably, the HCV patients with lower total cholesterol had worse survival (Thuluvath & John, 2003). In our study we have found that BMI is directly associated with diabetes, which corroborates the findings of Mehta *et al*. (2000).

In conclusion there was a strong correlation between HCV infection and DMI on the basis of epidemiological and biochemical analysis. HCV is a predictor of progression to different abnormalities in the patients with diabetes and renal disease. As both diabetes and HCV are more common among developing countries and NIDDM is considered to be the number one cause of ESRD, retinopathy and neuropathy, it is important to determine the mechanisms by which HCV may worsen these diseases. Medical practitioner should be aware of the increased risk of progression to ESRD in HCV patients having diabetes and should pay due attention to other risk factors, such as blood pressure, neuropathy, retinopathy and heart disease.

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