DOI: 10.14260/jemds/2015/166

ORIGINAL ARTICLE

PREVALENCE OF DIABETES MELLITUS TYPE 2 IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION

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HOW TO CITE THIS ARTICLE:
Ranjeet Kaur, Gurinder Mohan, Narotam Bhalla, Baldeep Kaur. "Prevalence of Diabetes Mellitus Type 2 in Patients with Chronic Hepatitis C Virus Infection". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 07, January 22; Page: 1184-1196, DOI: 10.14260/jemds/2015/166

ABSTRACT: BACKGROUND: There is a growing body of literature on the relationship of Hepatitis C Virus (HCV) infection and diabetes mellitus type 2 as its unique extrahepatic manifestation. This association was for the first time made by Allison et al. in 1994.[1] Since then a number of observational studies have been published on the prevalence of diabetes in HCV infection and also the link between association of cirrhosis with diabetes mellitus. **AIMS**: To study the prevalence of diabetes mellitus type 2 in patients diagnosed to have chronic hepatitis C virus infection. To compare it with the prevalence of diabetes mellitus type 2 in general population. **SETTINGS AND DESIGN:** A case control study. Participants were the subjects attending the OPD/ indoor of Sri Guru Ramdas Institute of Medical Sciences and Research, Amritsar. **PATIENTS AND METHODS:** 50 patients older than 18 years, with chronic HCV infection confirmed by ELISA, were investigated for their blood counts, LFTs, prothrombin time, serum proteins, glycosylated hemoglobin levels and abdominal ultrasonography after applying the exclusion criteria. Detailed clinical examination was done to assess for signs of encephalopathy and ascites. An equal number of age and sex matched, HCV seronegative patients with normal liver function tests were taken as controls. The prevalence of diabetes mellitus was then determined among the two groups. A relationship between HCV and Diabetes mellitus type 2 was then established. **STATISTICAL ANALYSIS USED:** Data was expressed as mean + SD. For categorical variables a chi square test was applied and p value was calculated. For the comparison of continuous data, the student t – test was used. Probability levels less than 0.05 were considered significant. **RESULTS:** 50% (25 out of 50) patients with chronic hepatitis C infection were diabetic while 30% (15 out of 50) of the controls were diabetic. The difference was statistically significant (p=0.041). Further, of the 50 cases, 22 had no evidence of cirrhosis on ultrasonography, and 28 had features of cirrhosis. Among the patients with cirrhosis, 6 belonged to Child Pugh class (CPC) - A and 22 belonged to Child Pugh Class- B. The percentage of diabetics in these 3 groups (normal, CPC-A and CPC-B) were 40.9%, 50% and 59.1% respectively. **CONCLUSIONS:** The study strengthens the association of HCV infection with diabetes mellitus as its common extrahepatic manifestation and shows increasing prevalence of DM type 2 with increasing severity of liver parenchymal injury. This alerts us to screen the HCV positive patients for diabetes mellitus type 2 and prevent combined complications and morbidity.

KEYWORDS: Hepatitis C virus, Diabetes Mellitus type 2, extrahepatic.

INTRODUCTION: Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide.[2] The long-term hepatic impact of chronic HCV infection is highly variable, with pathological conditions ranging from minimal hepatic changes to chronic hepatitis, extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC).[3]

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Although HCV mainly targets the liver, it has become interestingly evident that HCV can induce damage of many organs. Cacoub et al.[4] reported that 38% of patients with HCV would manifest at least one extrahepatic manifestation during the illness. Extrahepatic (EH) manifestations associated with HCV infection include endocrinological manifestations such as diabetes mellitus (DM)[5] and thyroiditis,[6] rheumatologic manifestations such as arthralgias, arthritis[7] and cutaneous manifestations like essential mixed cryoglobulinemia, porphyrea cutanea tarda, lichen planus, sjogren syndrome,[8] and others like glomerulonephritis[9] and metabolic syndrome.[10]

Diabetes Mellitus Type 2 is a major public health problem worldwide as people become more obese and live a more sedentary lifestyle.[11] This is in agreement with studies on T2D in non-infected individuals as well as patients infected with HCV genotypes. The following risk factors are strongly associated with Diabetes Mellitus Type 2: family history, body fat distribution, age, sex, smoking, and physical activity.[12] Several studies from different parts of the world have found that 13% to 33% of patients with chronic HCV have associated diabetes, mostly type 2 DM.[13]

Various pathogenic mechanisms have been studied for the diabetogenic action of HCV. Honeyman et al. found that HCV could trigger an immune reaction against the β-cells by molecular mimicry, because HCV shares regional amino acid homology with GAD autoantibody (GADA), one of the main islet cell antigens.[14] Direct damage to beta cells of pancreas is the another proposed mechanism. Laskus et al.[15] documented the presence of HCV-RNA in the pancreas acinar cells and in the epithelial cells of the pancreatic duct. Mendler MH et al speculated that iron stores are the link between HCV infection and diabetes,[16] while hepatic steatosis may also contribute to HCV-associated diabetes by impairing the insulin's ability to lower hepatic glucose production and favoring liver fibrosis.[17]

This association between HCV infection and diabetes was for the first time made by Allison et al. in 1994 and was formally tested by a retrospective review of 100 consecutive adult patients with cirrhosis undergoing assessment for liver transplantation. Of the 34 patients with hepatitis C virus-related cirrhosis, 17 (50%) had diabetes mellitus, in contrast to just six (9%) of the 66 patients with cirrhosis unrelated to hepatitis C virus (chi2 = 19.1, $p < 0.0001$) with an odds ratio for hepatitis C virus by diabetes mellitus status 10.0 (95% confidence interval 3.4 to 29.3).[18]

In an another Egyptian case control study by Eman I Elhawary et al. 289 HCV patients older than 18 were selected as cases. Also, 289 healthy controls were included. Out of 289 HCV cases, 40 (13.84%) were diabetic. Out of 289 healthy controls, 12 (4.15%) were diabetic.[19] Similarly in a study by Chehadeh et al.[20] study population consisted of 181 HCV positive cases and 170 HCV negative controls. The prevalence of type 2 diabetes among the cases was 39.8%.

Given the high spreads of Metabolic Syndrome and Chronic Hepatitis C, the chances of coexistence of these two conditions in a single patient are elevated. Nevertheless, this overlap is not simply coincidental, but many experimental[21] and clinical[22] studies have suggested how HCV infection itself seems to be able to perturb glucose homeostasis, leading to hepatic and extrahepatic Insulin resistance. The association of hepatitis C infection and diabetes is present, in fact, even before the onset of cirrhosis[23,24] and diabetes does not associate with other viral conditions such as hepatitis B.[25] The high prevalence of diabetes in HCV-infected patients, and its occurrence at early stages of hepatic disease, suggest that screening for glucose abnormalities should be indicated in these patients.

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The correlation is not unidirectional as chronic HCV infection is able to influence glucose and lipid metabolism and thus to perturb the metabolic homeostasis of the host leading to extrahepatic consequences. On the other hand the risk of progression from chronic HCV infection to cirrhosis and its clinical outcomes is highly variable and hyperglycemia, is believed to accelerate disease progression and to impact the likelihood of sustained virological response (SVR) after pegylated interferon/ribavirin therapy.[26]

The rationale behind this study is to find out the prevalence of type 2 diabetes in those patients who have chronic hepatitis C virus infection in comparison to general population and to establish the co-relation between stage of infection and type 2 diabetes mellitus in the seropositive HCV patients.

MATERIALS AND METHODS: In this study, a total of 50 ELISA positive chronic hepatitis C patients aged more than 18 years attending the OPD/ Indoor of SGRDIMSAR for routine health checkup formed the case group. An equal number of age and sex matched patients with normal liver function tests, no serological evidence of HCV served as the control group.

After taking relevant history and consent of the patient, fasting and random blood sugar levels were done as a screening tool to diagnose Diabetes Mellitus. Patients already diagnosed diabetics whether or not on therapy were also included in the study.

According to the American Diabetes Association criteria[27] patients were assigned a diagnosis of Diabetes Mellitus if;

1. HBA1C>=6.5% or,
2. fasting plasma glucose greater than 126 mg/dl; fasting is defined as no calorie intake for at least 8 hours, or
3. 2-h plasma glucose>=200mg/dL (11.1mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose >=200 mg/dL (11.1 mmol/L).

The diagnosis of HCV infection was made if patients were positive for anti-HCV antibody by second/third generation microparticle enzyme immunoassay test. Serological analysis for the detection of anti-HCV antibodies was carried out using accurate rapid immunochromatographic kits. Positive cases were later confirmed by using third generation ELISA kit (Eliscan^TM HCV by Diagnova) for the qualitative determination of antibodies to Hepatitis C Virus in human serum or plasma.

All patients were subjected to detailed history taking including demographic data(age, sex, family history of diabetes, history of alcohol intake), clinical examination and laboratory examination which included haemoglobin level, fasting and post prandial blood glucose, liver profile, serum proteins, glycosylated haemoglobin and ultrasound abdomen.

RESULTS: Of the 100 patients included in the study, 54% were females and 46% were males. 74% patients were from rural area while 26% belonged to urban area. 50 patients were HCV seropositive and served as cases. The remaining 50 were HCV seronegative and served as controls.

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a) **CASES AND CONTROLS:** The comparison between cases and the controls showed that the mean age of cases was 49.88 + 13.709 years while the mean age of controls was 50.74 + 14.267 years which was higher than the cases but the difference was not statistically significant (p = 0.7592). The mean BMI of cases was 24.5592 + 2.736 kg/ m^2 and 40 % (20 out of 50) of the cases had BMI > 25 kg/ m^2 while the mean BMI of the controls was 23.3546 + 2.997 kg/m^2 and only 24 % (12 out of 50) controls had BMI > 25 kg/m^2. The difference of the mean BMI among the cases and controls was statistically significant (p = 0.0384)

52% (n= 26) of the cases were anaemic while only 38% (n= 19) controls were found to have anaemia. This difference was not found to be statistically significant (p= 0.16). The mean Hb of cases was 9.738+ 2.442 gm% while the mean Hb of the controls was 10.12 + 2.108 gm %. The difference of means was not statistically significant (p= 0.4045). 22 % (11 out of 50) of the cases were found to have thrombocytopenia which was statistically significantly higher than the control group (1 out of 50); (p= 0.004).

58 % (29 out of 50) of the cases had hypoalbuminemia (Serum albumin <3 gm/dl) as compared to 34 % (17 out of 50) of the controls. Statistically the difference was significant (p= 0.016). The mean serum albumin of the cases (3.056 + 0.8054) was significantly lower than the controls (3.43 + 0.9237); (p= 0.0334).

18% (n= 9) of the cases were found to have prolonged prothrombin time as compared to the 2% (n=1) of the controls and this difference is statistically significant (p= 0.008). The difference in the mean value of PT prolongation (in seconds) between the cases and control group was also statistically significant (p=0.003).

The thrombocytopenia, hypoalbuminemia and the prolongation of Prothrombin time could be explained by the underlying liver parenchymal injury in patients with chronic hepatitis C virus infection.

The prevalence of diabetes mellitus among the cases was 50% (25 out of 50) while the prevalence among the controls was 30 % (15 out of 50). The difference was statistically significant higher (p=0.041).

Among the cases it was found that the prevalence of diabetes increased with increasing severity of the underlying liver disease. 40.9% in the HCV seropositive patients without cirrhosis had diabetes mellitus which was higher than the percentage of diabetics in the HCV seronegative control group (15 out of 50; 30 %). 57.1 % of the HCV seropositive patients with cirrhosis had diabetes mellitus. Further among those having cirrhosis, 6 belonged to Child Pugh Class –A out of which 50% (n=3) had diabetes and 22 belonged to Child Pugh Class –B out of which 59.1% (n=13) were diabetic. This strengthens the relationship of increasing degrees of liver damage being associated with increasing risk of developing diabetes mellitus in these HCV infected patients.

b) **HCV SEROPOSITIVE DIABETICS AND HCV SEROPOSITIVE NON-DIABETICS:** Among the HCV seropositive group, diabetics had the mean age of 55.12+10.414 years while the mean age of non-diabetics was 44.64+14.767 years. The difference was found to be statistically significant (p = 0.0056). Among the diabetics, 60% (n= 15) of the patients had BMI > 25kg/m^2 while 40 % (n=10) had BMI <25kg/m^2. Among the non-diabetics, 20% (n= 5) of the patients had BMI > 25kg/m^2 while 80% (n=20) had BMI <25kg/m^2. The difference was found to be statistically significant (p = 0.004).

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Hypoalbuminemia was present in 68% (n=17) of the diabetics in comparison of 48% (n=12) of the non- diabetics (p=0.152). The mean serum albumin in the diabetics was 3.832 + 0.8335 gm/dl while in the non- diabetics, it was 3.28 + 0.7286 g/dl. The difference is statistically significant (p = 0.0481).

Similarly higher percentage of diabetics (24%) had prolonged prothrombin time than the non-diabetics (12%) but the results were statistically not significant (p=0.27).

Diabetics cases were more prone to have cirrhosis than the non- diabetic HCV cases. Cirrhosis was present in 64% (n=16) of the diabetic patients in comparison to 48% (n=12) of the non-diabetics. The difference was not statistically significant (p=0.25).

c) HCV SEROPOSITIVE DIABETICS AND NON-HCV DIABETICS: Further comparison was made between HCV seropositive diabetics and the non-HCV diabetics and we found that the mean age of HCV diabetics (55.12+10.414 years) was comparable to the mean age of diabetic controls (57.2+9.578 years) and thus not statistically significant (p = 0.53). Females represented 64% of the diabetic HCV cases and 60% of the diabetic non- HCV controls. This could be due to the higher percentage of females enrolled in our study.

The HCV diabetics had significantly higher percentage of patients with thrombocytopenia (p=0.04), hypoalbuminemia (p=0.033) and prolonged Prothrombin time (p=0.04) than the non-HCV diabetics which can be explained by the underlying liver parenchymal injury in the HCV group. As for the comparison of glycemic control between the two groups, the mean HBA1c of the HCV diabetics was 8.1+ 2.084 which was lower than that of the non-HCV diabetics (9.093 + 2.195; p = 0.16). This shows that HCV diabetics had better glycemic control than non-HCV diabetics but the result is not statistically significant and may be because of various confounding factors and warrants further investigation.

DISCUSSION: Diabetes mellitus is a unique extrahepatic manifestation of chronic hepatitis C virus infection. The link between the HCV and diabetes was first reported by Allison et al. in 1994.[1] Based on case-control studies, the prevalence of DM had been reported in 21% to 50% (a two- to ten-fold increase in prevalence) of patients with chronic HCV infection, which was significantly higher than that in the general population or among patients with other forms of liver diseases.[28] In our study the prevalence of Diabetes Mellitus in HCV positive patients was found to be 50% as compared to 30% in the HCV negative controls. In the Egyptian case- control study by Elhawary et al. 13.84% (40 out of 289) HCV cases had diabetes mellitus as compared to 4.15% (12 out of 289) of the HCV negative controls.[19] Similarly in a study by Chehadeh et al.[20] study population consisted of 181 HCV positive cases and 170 HCV negative controls. The prevalence of type 2 diabetes among the cases was 39.8%. Even higher prevalence of diabetes mellitus was found in the HCV positive patients when the study sample was taken from the transplant recepients. Al- Dosary et al found 40% subjects to be diabetic among HCV seropositive liver transplant recepients.[21] Similarly in a study in USA by Baid et al the prevalence of diabetes among HCV positive cases was 70 % (33 out of 44) as compared to 37% in the HCV negative controls.[21] Differences in the criteria employed in the diagnosis of DM, source of controls, case definition, sample size and underlying target population may explain much of this observed variability among the studies.

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SOCIODEMOGRAPHIC CHARACTERISTICS OF THE CASES AND CONTROLS: We found that HCV seropositive diabetics were older and more obese than the HCV seropositive non-diabetics. The mean age of HCV diabetics was higher than the mean age of HCV non-diabetics which is similar to the findings of Egyptian study by Elhawary et al.[19] where the mean age of HCV seropositive diabetic cases was 48.1+9.2 years and that of non- diabetic cases was 40.7+10.4 years. (Statistically significant difference, p = 0.001). In the study by Rouabhia S et al 47.6 % of the HCV seropositive diabetics had BMI > 25kg/m^2 while in the HCV positive non-diabetics 7.6% had BMI >25kg/m^2 and the difference was statistically significant.[30]

Diabetes was more prevalent in females than the males which could be due to higher number of females enrolled in the study. Also diabetes was more prevalent in the urban as compared to the rural population which can be explained by the more sedentary lifestyle and lack of physical activity among the urban population.

LIVER STATUS: We found that the prevalence of Diabetes Mellitus was 40.9 % in the HCV positive patients without evidence of liver cirrhosis. It was 50 % in patients with cirrhosis belonging to CPC-A and was 59.1% in those belonging to CPC-B. Thus the prevalence of diabetes mellitus increases with the increasing severity of the liver injury. Knobler et al. evaluated a group of 45 patients with chronic HCV infection in whom cirrhosis had been carefully excluded. 90 patients without HCV infection served as controls. Higher prevalence of type 2 diabetes was found in patients infected with HCV (33%) as compared to the HCV seronegative controls (5.6%).[24] Further findings are also in consistence with the Southeast Asian study by Memon S et al., where out of the total number of the participants (n= 361); 211(58.4%) had cirrhosis, while 150(41.6%) were non-cirrhotic HCV seropositives. The study found that 81(38.4%) had diabetes in the group with cirrhosis as compared to 33(22%) in the group without cirrhosis.[31] Rouabhia S et al. also found that prevalence of DM increased progressively and significantly with the fibrosis stage from 14.3% in stage F0 to 32.8% in F2 and 62.5% in stage F4.[30]

HEMATOLOGICAL PARAMETERS: Blood picture did not differ significantly between the 2 HCV groups. Anaemia was present in 64% (n= 16) of the diabetic patients while it was present in only 40 % (n= 10) of the non- diabetic patients. But the difference was statistically not significant (p= 0.089). Similarly thrombocytopenia was present in 24% (n=6) of the diabetic patients as compared to 16 % (n=4) of the non-diabetic patients (statistically not significant; p=0.48). In our study we found that HCV seropositive patients with diabetes had significantly lower values of mean serum albumin and significantly higher prolongation of prothrombin time as compared to the HCV seropositive patients without diabetes. Memon S et al also found the similar results with mean serum albumin in HCV positive diabetics to be 3.22+ 0.71 and in HCV positive non-diabetics to be 3.44 + 0.68 (statistically significant difference, p= 0.004).[31]

Our study did not show increased levels of transaminases (SGOT and SGPT) and serum bilirubin in the diabetic group as compared to the non-diabetic group. In contrast, the study by Elhawary et al. abnormal high ALT, high bilirubin values were more frequently seen among diabetic cases as compared to non- diabetic cases.[19]

HCV DIABETIC CASES VS NON-HCV DIABETIC CONTROLS: The comparison of HCV diabetics and the non-HCV diabetics showed no significant difference in age, gender variation and BMI. The former had significant higher percentage of patients with thrombocytopenia (p=0.04), hypoalbuminemia (p=0.033) and prolonged Prothrombin time (p=0.04) which can be explained by the underlying liver disease. El-kafrawy et al. also did not find any significant difference between hemoglobin of patients in two groups i.e. HCV positive with diabetes and HCV negative with diabetes but the mean platelet count of the first group (172.2+52.6) was significantly lower than the second group (253.1+57.38); (p = 0.001). The study by El-kafrawy et al. also showed similar results for hypoalbuminemia and prolonged prothrombin time.[32]

CONCLUSION: In our study we found that the patients with chronic hepatitis C virus infection had a higher prevalence of Diabetes Mellitus than the controls. The risk of type 2 diabetes increases further if the HCV seropositive patient has cirrhosis. The presence of diabetes was found to effect the severity of liver parenchymal disease in the HCV seropositive patients as is evident from the markers of liver parenchymal injury which were markedly deranged in the HCV positive patients with diabetes as compared to both HCV positive patients without diabetes and HCV negative patients with diabetes. Advancing age and increased weight are important predictors of type 2 diabetes in HCV seropositive patients. It is necessary to screen earlier for the presence of type 2 diabetes mellitus and thus prevent development of comorbid complications and mortality through timely intervention.

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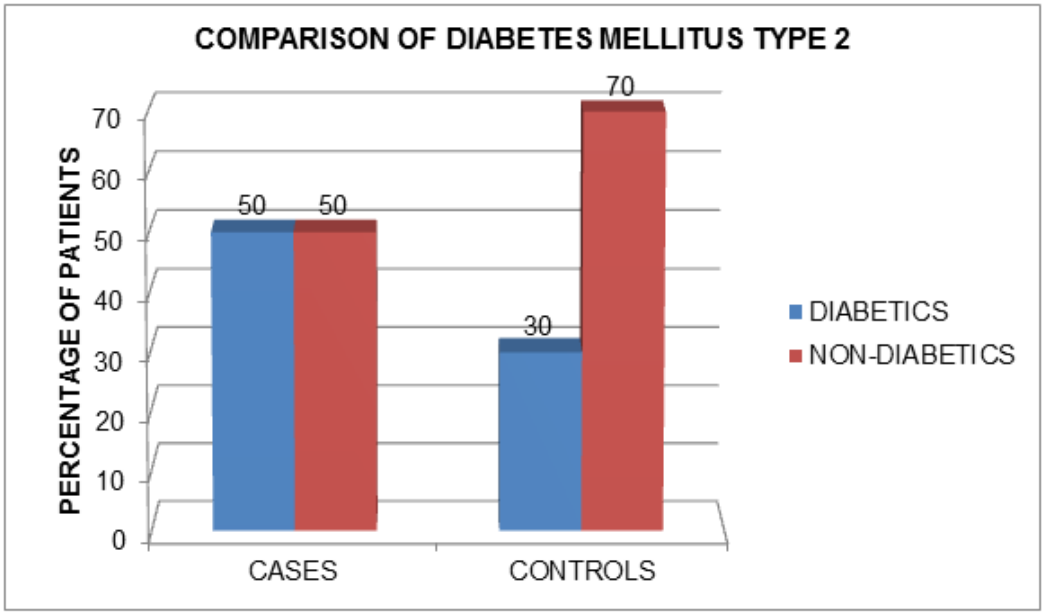
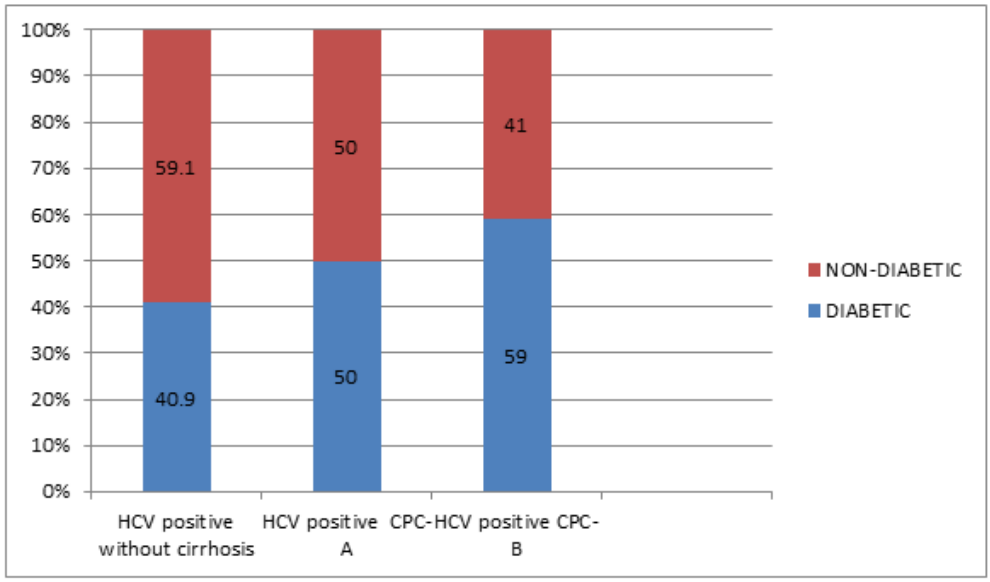


Graph 1: Showing comparison of the prevalence of Diabetes mellitus type 2 among the cases and the controls

DOI: 10.14260/jemds/2015/166



Graph 2: Showing the comparison of the prevalence of Diabetes Mellitus among various groups according the severity of liver parenchymal injury among the HCV seropositive patients

Parameter	Values	Cases	Controls	P value
Age-years	<40	8	8	1.00
	≥40	42	42	
Gender	Female	27	27	1.00
	Male	23	23	
Residence	Urban	15	11	0.362
	Rural	35	39	
Anaemia (gm%)	Hb<10gm%	26	19	0.16
	Hb>=10gm%	24	31	
Thrombocytopenia (lakhs/ cumm)	PLATELETS<= 1lakh/ cumm	11	1	0.002
	PLATELETS> 1 lakh/ cumm	39	49	
Hypoalbuminemia (gms/dl)	SERUM ALBUMIN <=3	29	17	0.016
	SERUM ALBUMIN >3	21	33	
PT prolongation (seconds)	>=3 sec	9	1	0.008
	<3 sec	41	49	
BMI—kg/m2	>=25 kg/m2	20	13	0.137
	<25 kg/m2	30	37	
Family history of diabetes	Yes	15	15	1.00
	No	35	35	
Marital Status	Married	46	47	0.69
	Unmarried	4	3	

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Diabetes	Yes	25	15	0.041
	No	25	35	
Ultrasound status of liver	Cirrhosis	28	0	0
	No cirrhosis	22	50	

Table 1: Comparison of variables among cases and controls in study population

Parameter	Value	HCV Cases		
		Diabetic	Non Diabetic	P value
Age-years	<40	1	7	0.021
	≥40	24	18	
Gender	Female	16	11	0.156
	Male	9	14	
Residence	Urban	10	5	0.123
	Rural	15	20	
Anaemia (gm %)	<10gm%	16	10	0.089
	>10gm%	9	15	
Thrombocytopenia (per cumm)	Platelet < 1 lakh	7	4	0.306
	Platelet > 1 lakh	18	21	
T Bilirubin – mg/dl	> 1.5 mg/dl	2	7	0.066
	<=1.5 mg/dl	23	18	
SGOT- U/L	> 74	6	11	0.136
	<=74	19	14	
SGPT- U/L	>130	2	2	1
	<=130	23	23	
Hypoalbuminemia (gm/dl)	S.Albumin <=3	17	12	0.152
	S.Albumin >3	8	13	
PT prolongation (secs)	>=3secs	6	3	0.27
	<3secs	19	22	
Liver status	Cirrhosis	17	12	0.152
	No cirrhosis	8	13	
BMI—kg/m2	>=25 kg/m2	15	5	0.004
	<25 kg/m2	10	20	
Family history of diabetes	Yes	9	6	0.355
	No	16	19	

Table 2: Comparison of variables among the 'HCV seropositive diabetic' and 'HCV seropositive non-diabetic' groups

DOI: 10.14260/jemds/2015/166

Parameter	Value	Diabetes Cases		
		HCV Seropositive	HCV Seronegative	P value
Age—years	<40	1	0	0.433
	≥40	24	15	
Gender	Female	16	9	0.8
	Male	9	6	
Residence	Urban	10	4	0.392
	Rural	15	11	
Anaemia – gm%	<10gm%	16	7	0.283
	>=10gm%	9	8	
Thrombocytopenia (per cumm)	Platelet <= 1 lakh	7	0	0.024
	Platelet > 1 lakh	18	15	
T Bilirubin- mg/dl	> 1.5 mg/dl	2	0	0.261
	<=1.5 mg/dl	23	15	
SGOT- U/L	> 74	6	0	0.04
	<=74	19	15	
SGPT- U/L	>130	2	0	0.261
	<=130	23	15	
Hypoalbuminemia- gm/dl	S.Albumin <=3	17	5	0.033
	S. Albumin >3	8	10	
PT prolongation – secs	>=3 secs	6	0	0.04
	<3 secs	19	15	
Liver status	Cirrhosis	17	0	0
	No cirrhosis	8	15	
BMI—kg/m^2	>=25 kg/m^2	15	6	0.22
	<25 kg/m^2	10	9	
Family history of diabetes	Yes	9	8	0.283
	No	16	7	

Table 3: Comparison of variables between 'HCV seropositive diabetics' and 'HCV seronegative diabetics'

DOI: 10.14260/jemds/2015/166

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Date of Submission: 17/12/2014.
Date of Peer Review: 18/12/2014.
Date of Acceptance: 13/01/2015.
Date of Publishing: 21/01/2015.