

A Cross-sectional Study of Prevalence of Diabetes among Patients with Hepatitis C

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ABSTRACT

Objective: To estimate the prevalence of type 2 diabetes in patients with chronic hepatitis C.

Study design: Descriptive cross-sectional

Study setting: Department of Medicine, Aziz Fatimah Medical and Dental College, Faisalabad and Mohtrama Benazir Bhutto Shaheed Medical College / Divisional Headquarters Teaching Hospital, Mirpur Azad Kashmir.

Study duration: Six months from April 2021 to September 2021.

Methods: Study participants were recruited from the outpatient department at Aziz Fatimah Medical and Dental College, Faisalabad and Mohtrama Benazir Bhutto Shaheed Medical College / Divisional Headquarters Teaching Hospital, Mirpur Azad Kashmir for duration of six months from April 2021 to September 2021. All demographic, medical and laboratory information were collected. Descriptive statistics, chi-square tests of independence were used to analyse the data.

Results: Out of 300 hepatitis C patients (53% males, 47% females), overall, 26% (77 out of 300) were found to have diabetes. When characteristics of patients with and without diabetes disease were compared using χ^2 tests, we could not find any statistically significant relation of gender, BMI, hepatitis C disease duration, family history of diabetes and Child-Pugh classification of liver disease with prevalence of diabetes. Younger, middle-aged (30-50 years) patients had significantly higher prevalence of diabetes compared to older (51-70 years) aged patients (28% vs. 13%, $p = 0.022$).

Conclusion: 1 in 4 hepatitis C patients also manifest co-morbidity of diabetes. Having a younger or middle age (≤ 50 years) appears to contribute to diabetes prevalence in hepatitis C patients, however, the study sample comprises around 4 in 5 patients aged 30-50 years. Glucose intolerance and diabetes risk assessment, and early non-pharmaceutical management (probably uptake of healthy eating and physically active behaviour) among hepatitis C patients is warranted if complications are to be prevented.

Key Words: Hepatitis C, diabetes, Child-Pugh class

Key Points

- **Question:** What is the prevalence of type 2 diabetes in patients with chronic hepatitis C in Faisalabad setting?
- **Findings:** In this one-centre study that included 300 patients with ELISA and PCR confirmed hepatitis C disease presented in the OPD of Aziz Fatimah Medical and Dental College, Faisalabad and Mohtrama Benazir Bhutto Shaheed Medical College / Divisional Headquarters Teaching Hospital, Mirpur Azad Kashmir, nearly 26% of patients had type 2 diabetes. Among those patients with chronic hepatitis C disease, having type 2 diabetes was associated with much greater odds of having under 50 years age.

Meaning: Patients with chronic hepatitis C warrant glucose intolerance risk assessment and monitoring for progression of pre-diabetes/ diabetes, liver disease and the consequences of both.

INTRODUCTION

Diabetes mellitus is a growing global health issue and is a major cause of morbidity (e.g., blindness, cardiovascular complications, renal failure and lower-limb amputation) and mortality, accounting for 1.5 million deaths in 2019 and 1 in 11 individuals worldwide are living with diabetes.¹ Chronic hepatitis C is also a growing challenge and increases risk of liver cirrhosis and cancer, with hepatitis C attributed cirrhosis and hepatocellular carcinoma accounting for almost 290,000 deaths in 2019 and 58 million people in the world have chronic hepatitis C.² Besides these hepatic manifestations of cirrhosis and hepatocellular carcinoma, hepatitis C virus (HCV) is associated with extrahepatic manifestation including glucose metabolism disturbance.³

This impaired glucose metabolism can be either a classical type 2 diabetes if develops before cirrhosis onset or the hepatogenous diabetes, i.e. a manifestation of hepatic insufficiency which develops after cirrhosis onset.⁴ The HCV epidemic is growing the burden of disease.⁵ Therefore, it can be seen that both diabetes and chronic hepatitis C diseases can have lifelong health impacts.

The comorbidity of hepatitis C and type-2 diabetes mellitus is often found clinically. Several epidemiological studies have reported a significant association between hepatitis C and diabetes across developed and developing countries.⁶ Among HCV infected individuals, prevalence of type-2 diabetes is three times more frequent than non-infected individuals in USA,⁷ 13.27 % in Ottawa, Canada,⁸

and 25.4% in Egypt.⁹ Pooled estimate from a meta-analysis of 14 studies suggests that individuals with HCV infection have two times the odds of diabetes compared to individuals without HCV infection (odds ratio (OR) = 2.03 [95% confidence interval (CI): 1.52-2.54]).¹⁰ On following-up a cohort of individuals who underwent hepatitis C testing in British Columbia, Canada, individuals who diagnosed HCV infection had a higher incidence rate of type 2 diabetes compared to individuals who did not diagnose HCV infection.¹¹

Some potential direct and indirect biological mechanisms explain the association between hepatitis C and diabetes. This association may be attributed to (i) HCV proteins-promoted insulin resistance via down-regulation of glucose transporters and insulin receptors,^{3, 6, 12, 13} (ii) HCV-associated autoimmune disorders and HCV-triggered inflammatory mediators lead to diabetes⁶ and (iii) hepatitis C treatment-induced diabetes (both type 1 and type 2) e.g. interferon alpha elevate interleukin-1 which is cytotoxic to pancreatic islet cells.^{6, 13} The coexistence of chronic hepatitis C and type 2 diabetes accelerates progression of liver fibrosis and hepatocellular carcinoma.^{3, 6}

The prevalence and association between hepatitis C and diabetes has also been observed in reverse direction – meaning that diabetes can also increase the risk of HCV infection. Prevalence of HCV infection in diabetic patients is 2.42% in Southeast and Northeast region of Brazil,¹⁴ 13.3% in South-west Nigeria¹⁵ and 19% in Myanmar.¹⁶ Compared to healthy individuals without non-autoimmune diabetes, the summary estimate from a meta-analysis of 43 studies indicates that individuals with non-autoimmune diabetes have 3.6 times the likelihood of having HCV infection (OR = 3.6 [95% CI: 2.7-4.9]).¹⁷ This reverse causality can be described through exposure to bloodborne HCV virus in diabetic patients during blood extraction for glucose monitoring and insulin administration.

Epidemiological studies worldwide suggest that chronic hepatitis C can increase the risk of having the comorbidity of diabetes and having diabetes can make people vulnerable to get HCV infection – suggesting a bidirectional association between hepatitis C infection and diabetes. In Pakistan, comparable statistics on the prevalence and association have also been reported in both directions, with an estimated HCV prevalence by diabetes status is 13.7% in Multan¹⁸, and estimated type 2 diabetes prevalence by HCV infection status is 26.4% in one public tertiary care facility in Peshawar¹⁹ and 31.5% in one private tertiary care facility in Hyderabad.²⁰

Chronic hepatitis C – if left untreated or not treated successfully – can have debilitating effects and comorbid diabetes can augment these effects, however, studies about diabetes prevalence in patients with chronic hepatitis C remain scarce in Faisalabad to evaluate precise estimates. Therefore, our objective was to determine the prevalence of diabetes mellitus in hepatitis C individuals from one outpatient centre and to identify potential risk factors for diabetes among HCV infected individuals. Knowing about the prevalence of diabetes among hepatitis C sample population can help us to understand the demands on health services to manage this disease in our local setting.

MATERIAL AND METHODS

Study design and setting: The research was designed as a descriptive cross-sectional study and conducted at the Department of Medicine, Aziz Fatimah Medical and Dental College, Faisalabad and Mohtrama Benazir Bhutto Shaheed Medical College/ Divisional Headquarters Teaching Hospital, Mirpur Azad Kashmir.

Sampling and Participants: The World Health Organization (WHO) sample size calculator was utilised to calculate the required sample size of 300 participants to estimate diabetes prevalence among chronic HCV infected individuals. Inputs were the estimated value for the proportion 0.2647 (26.47%),¹⁹ the 0.95 (95%) level of confidence and 0.05 (5%) precision of the estimate.

This study sample was drawn from all consecutive outdoor hepatitis C patients between April 2021 to September 2021 who had met the inclusion criteria. We included both male and female adults aged 30 to 70 years who had enzyme-linked immunosorbent assay (ELISA) confirmed and polymerase chain reaction (PCR) confirmed hepatitis C for at least last six months. People were excluded if they had chronic hepatitis B, human immunodeficiency virus (HIV) infection, clinical decompensated liver cirrhosis or cancer, had already been identified diabetic. All participants provided written informed consent; this research was approved by the ethical review committee of the Aziz Fatimah Medical and Dental College, Faisalabad and Mohtrama Benazir Bhutto Shaheed Medical College/ Divisional Headquarters Teaching Hospital, Mirpur Azad Kashmir.

Procedures: Potential participants underwent a series of in-person assessments for study eligibility. To assess diabetes blood sample was collected and sent to the hospital pathology laboratory. All demographic, medical and laboratory data including age in years, gender, body mass index (BMI), hepatitis C diagnosis, duration of hepatitis C disease in years, family history of diabetes, diabetes status and Child-Pugh class of liver disease were retrieved and recorded on a proforma by first researcher (K.A.).

Measures: Hepatitis C antibody enzyme linked immunosorbent assay (ELISA) testing and hepatitis C ribonucleic acid (RNA) polymerase chain reaction (PCR) testing were used to identify patients with chronic hepatitis C.

To be diagnosed with diabetes, an individual had to have fasting blood sugar (FBS) level >110 mg/dl or random blood sugar (RBS) level >200mg/dl two hours after a meal.

To assess the chronic liver disease, Child-Pugh classification was utilised. Scores were calculated according to standard conventions and categorised into their relative classes.

Statistical analyses: Descriptive statistics were used to analyse both demographic and clinical characteristics. Frequency and percentages were calculated for both quantitative and categorical variables; and mean with standard deviation and median were calculated for quantitative variables including age, BMI and hepatitis C disease duration. These three quantitative variables were dichotomized into age ≤ 50 or > 50 years, BMI ≤ 27 or > 27 kg/m² and disease duration ≤ 5 or > 5 years. The patients were grouped depending on their diabetes diagnosis and

analysed on the basis of age, gender, BMI, hepatitis C duration, family history of diabetes and Child-Pugh classification of liver disease. The data were analysed using chi-square test with stratification for effect measure modification and/ or confounding factors (age, gender, BMI, disease duration, family history of diabetes, Child-Pugh class of liver disease) at 5% level of significance (i.e., p -value ≤ 0.05). Where possible, unadjusted prevalence odds ratio (POR) with 95% confidence intervals (CI) as measure of strength of association between patient characteristics and prevalence diabetes were also computed and considered. All analyses were conducted in SPSS V-21.

RESULTS

A total of three hundred patients who had been notified as being positive for both hepatitis C antibody and hepatitis C PCR testing were identified, with a mean age of 43.07 ± 7.88 (range 30-70) years, mean BMI of 27.55 ± 3.03 kg/m², mean disease duration of 5.95 ± 2.38 years with 47% being women. Table I describes the summary characteristics of the study participants. Younger patients (30-50 years) were four times more frequent than older (51-70 years) patients (82% vs. 18%). Over one-fourth (or 29%) of the study sample population reported family history of diabetes.

Table 1: Summary Statistics on Sample of (n=300) Hepatitis C Participants

Characteristics	n	%	Mean \pm SD [Median]
Age (years)	300	100	43.01 ± 7.88 [42]
30-50	247	82	
51-70	53	18	
Gender			
Female	141	47	
Male	159	53	
Duration of disease (years)			5.95 ± 2.38 [5]
≤ 5	171	57	
>5	129	43	
BMI (kg/m ²)			27.55 ± 3.03 [26.5]
< 27	151	50	
≥ 27	149	50	
Family history of DM			
Yes	87	29	
No	213	71	
Diabetes			
Yes	77	26	
No	223	74	
Child-Pugh Class			
A	151	50.3	
B	82	27.3	
C	67	22.3	

The overall prevalence of diabetes was 26% (77 out of 300 patients). Table II shows characteristics of hepatitis C participants by their diabetes status. Younger, middle-aged (30-50 years) patients had higher prevalence of diabetes compared to older (51-70 years) aged patients (28% vs. 13%). Age ≤ 50 years was significantly associated with diabetes prevalence compared to those with age over 50 years age ($p = 0.022$, POR = 2.6, 95% CI = 1.12-6.03). However, patients with and without diabetes did not differ significantly on other demographic (e.g., gender) and

clinical characteristics including disease duration, Child-Pugh class of liver disease.

Table 2: Characteristics of hepatitis C participants by diabetes mellitus

Variable	DM + (n=77)	DM - (n=223)	p-value
Age (years)			
≤ 50	70	177	0.022
>51	7	46	
Gender			
Female	37	104	0.83
Male	40	119	
BMI (kg/m ²)			
>27	42	107	0.321
≤ 27	35	116	
Family history of DM			
Yes	27	60	0.174
No	50	163	
Hepatitis C duration (years)			
≤ 5	47	124	0.406
>5	30	99	
Child-Pugh Classification of liver disease			
A	35	116	0.61
B	23	59	
C	19	48	

A weak association was seen between family history of diabetes and diabetes prevalence among hepatitis C patients; however, it did not reach statistical significance ($p = 0.174$, POR = 1.46, 95% CI = 0.84-2.55). Higher BMI (> 27 kg/m²) was also insignificantly weakly associated with diabetes prevalence ($p = 0.321$, POR = 1.30, 95% CI = 0.77-2.19) compared to those with a lower BMI (≤ 27 kg/m²). Similarly, shorter (≤ 5 years) or longer (> 5 years) hepatitis C disease duration did not explain the difference ($p = 0.406$, POR = 1.25, 95% CI = 0.74-2.12).

DISCUSSION

We investigated the prevalence of diabetes in hepatitis C individuals in one local outpatient centre. Almost one-fourth (or 26%) of the study sample population of hepatitis C individuals have comorbidity of diabetes. Hepatitis C patients with ≤ 50 years age have 2.6 times the likelihood of prevalent diabetes compared to hepatitis C patients with over 50 years age. This estimator can be unbiased, however, may not be consistent because almost 4 in 5 (82%) hepatitis C patients were ≤ 50 years in this study sample. Gender, BMI, hepatitis C disease duration, family history of diabetes and Child-Pugh classification of liver disease could not appear to influence diabetes prevalence among hepatitis C patients.

Strength included our study employed objective measures of both hepatitis C and diabetes. The current study has limitations. Firstly, we restricted our sample, generalisability is limited to hepatitis C individuals seeking outpatient allopathic health service. Key risk factors, such as middle, older age, higher BMI, family history of diabetes are independent predictors of diabetes in general population²¹ and HCV-infected sample⁶ and at least five years of hepatitis C disease duration contributes to peripheral insulin resistance and resultant type 2 diabetes;³ however, these factors could not explain any difference in

this current clinically-based sample of hepatitis C patients – suggesting our sample size may also not have statistically enough power to detect such real differences. Moreover, dichotomisation of continuous variables (e.g., age, BMI and hepatitis C disease duration) in current analysis may have lost statistical information to detect an association between one unit change in variable and outcome.

Lastly, the inherent issue of reverse association in cross-sectional study hinders conclusion – hepatitis C infection leads to diabetes development as an extrahepatic manifestation or individuals with diabetes may be more likely to get HCV during assisted blood glucose monitoring and insulin administration through contaminated equipment (e.g., shared fingerstick devices, blood glucose meters, insulin pens). This can be seen in studies which have been identified outbreaks of hepatitis B virus (HBV) infection associated with assisted monitoring of blood glucose level and/ or administration of insulin.²² Although evidence identifies outbreaks of HBV, we can therefore deduce risk of infection for any bloodborne virus, such as HBV, HCV and HIV. This can be probably mediated through use of shared devices or assistance in blood glucose assessment and/ or insulin injection without compliance to hygiene practice of infection control.²³

Research in this area would also benefit by examining and taking account of social determinants of health – non-medical confounding factors that influence health, such as education and health literacy, socioeconomic status, unemployment, working conditions, housing and neighbourhood (e.g., walkability and sanitation) and accessibility to affordable medical care services²⁴ – that can potentially increase the risk of diabetes development in chronic hepatitis C cohort. Furthermore, interventional research in preventing or delaying diabetes among hepatitis C patients should also be focused on modification of lifestyle behavioural factors. This is because liver becomes progressively insufficient to metabolise antidiabetic drugs²⁵ which leads to drug-induced adverse events and further challenges.

The current study provides some important implications for clinical practice. First and foremost, it provides precise estimate of diabetes in hepatitis C individuals and the necessity of its early diagnosis. It also emphasises the importance for hepatitis C patients to receive diabetes treatment, the receipt of treatment for chronic diabetes management does not interfere the requirement of hepatitis C treatment. The bidirectional relationship between hepatitis C and diabetes – insulin resistance can be worsened by HCV infection and HCV attributed chronic liver disease can be worsened by diabetes – share the common goal of both treatments i.e., improved quality and functionality. Diabetes is a modifiable outcome. This is because evidence suggests diabetes can be prevented and/ or delayed by complying a healthy diet and engaging in regular exercise.²⁶ Therefore, hepatitis C patient counselling on uptake of healthy eating and physically active behaviour can be beneficial to prevent consequences.

CONCLUSION

We conclude that nearly 1 in 4 (26%) of the hepatitis C patients also suffer with diabetes. Optimal public health

intervention to alleviate the excess prevalence of diabetes in hepatitis C infected individuals will depend on understanding the factors that underlie these differences in health status.

Conflict of interest: None to declare.

Disclosure: Being part of a dissertation.

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