Association of Type 2 Diabetes Mellitus with Chronic Hepatitis C Virus Infection

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ABSTRACT

Objective: To determine the association of type 2 diabetes mellitus with chronic hepatitis C virus (HCV) infection.
Study Design: Case control study.
Place and Duration of Study: Combined Military Hospital, Peshawar Pakistan, from Jun 2017 to Jun 2018.
Methodology: After fulfilling the inclusion criteria, 190 patients were enrolled in the study and divided into two equal groups. The patients of either gender with positive anti-hepatitis C antibodies/PCR for HCV, ribonucleic acid (RNA) were included as cases and apparently healthy individuals reporting for blood donation were included as controls. Plasma glucose was tested by hexokinase enzymatic method using Advia 1800 after 8 hours fast. Then the association between the two major diseases was observed.
Results: Patients in the case and control groups had the mean age of 40.26 ± 8.05 and 40.29 ± 8.89 years respectively whereas body mass index in the case group was 26.60 ± 1.67 kg/m^2 and 26.05 ± 1.49 kg/m^2 in the control group. Mean duration of HCV infection was 7.03 ± 2.21 months in the case group. Mean serum ALT level was 46.81 ± 7.25 U/L in the case group and 28.43 ± 4.66 U/L in the control group. A total of 76.8% of patients in case group had been treated for HCV infection previously. Type 2 diabetes was seen in 38 (40%) cases and 19 (20%) controls (Odd Ratio=2.60; p=0.002).
Conclusion: Type 2 diabetes mellitus is more frequent amongst HCV positive patients as compared to HCV negative patients.

Keywords: Association, Chronic liver disease, Hepatitis C virus, Type 2 diabetes mellitus.

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INTRODUCTION

Hepatitis C virus infection (HCV) is a common cause of chronic liver disease (CLD) worldwide involving more than 180 million people about 2.8% population globally.[1] About ten million people are infected in Pakistan. There are seven genotypes with 67 subtypes of hepatitis HCV.[2] HCV genotypes not only have epidemiological implications but also seriously affect treatment outcomes. In Pakistan, genotype 3a is the most common, seen in 58% cases, followed by genotype 3b (8%) and 2a (6%).[3] Almost 75-85% of patients having HCV develop liver cirrhosis followed by hepatocellular carcinoma, whereas only a few cases clear spontaneously.[4] Chronic HCV infection is now recognized as metabolic syndrome because it has tendency to affect multiple organ systems causing fatty liver (hepatic steatosis), insulin resistance and type 2 diabetes mellitus (DM), promoting atherosclerosis and cardiovascular diseases.[5] Sulehria *et al*, found that 28% HCV infected patients had type 2 diabetes, as compared to 8% in non -HCV infected patients.[6] HCV infection and diabetes mellitus (DM) are two major public health problems worldwide.[7] Patients with diabetes mellitus along with HCV disease have more chances of developing cirrhosis and hepatocellular carcinoma as compared to non-diabetic subjects. HCV causes insulin resistance either directly or indirectly, by affecting the signaling pathways of insulin receptor at cellular level. Insulin increases glucose uptake by binding to its receptor and then activating complex signaling pathways involving sequential activation of Insulin receptor substrate (IRS), phosphoinositide 3-kinase (PI3K) and protein kinase C. This process finally results in activation of glucose uptake after translocation of the glucose transporter type 4 (GLUT4) to the plasma membrane. Malfunction at any level of this pathway results in insulin resistance. Molecular mechanisms provide explanations for which HCV infection might increase the risk for development of type-II DM or worsen glycemic control in patients with established type-II DM. In normal circumstances, when insulin attaches to the insulin receptor on a hepatocyte, the nearby insulin receptor substrate 1 or 2 (IRS-1/ IRS-2) is phosphory-lated and associates with the insulin receptor, this in turn causes downstream activation of protein kinase B (AKT). The activated AKT causes the translocation of glucose transporter-4 to the cell surface, which then brings glucose into the

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hepatocyte. AKT also causes increased protein synthesis, increased glycogen synthesis, inhibition of lipolysis, and inhibition of hepatic gluconeogenesis.[8] HCV causes insulin resistance and obstruction of intracellular glucose uptake by prohibition of translocation of glucose transporter type 4 (GLUT-4) to cell membrane via its core protein and indirectly through inflammatory mediators like tumor necrosis factor alpha (TNF-α) production which affects these signaling pathways at multiple levels.

The prevalence of DM has been reported 11.77% in Pakistani population.[9] Multiple studies have been conducted in various parts of the world to find out association of DM with chronic HCV. Many of them suggest positive association, while a few negate this.[10] However, local literature on this subject is not abundant. We planned this study to determine the relationship between these two most prevalent health problems in our society as there is variable result of multiple studies done in various other populations. This study would provide local based evidence and stimulus to explore into the effects of treatment of chronic hepatitis C on glycemic control in addition to the advantages of strict glycemic control on progression of chronic HCV infection.

METHODOLOGY

This case control study was conducted at Combined Military Hospital Peshawar, from June 2017 to June 2018. Ethical Review Committee of Combined Military Hospital Peshawar approved the study protocol vide serial no 17. Sample size was calculated using WHO sample size calculator. Total sample size of 190 (divided into two equal groups) was calculated using WHO sample size calculator.

Inclusion Criteria: Adult patients of both genders with ages between 20-65 years were enrolled for this study. Patients with anti-HCV antibodies/polymerase chain reaction (PCR) for HCV RNA positive were considered as cases and apparently healthy individuals reporting for blood donations were considered as controls.

Exclusion Criteria: The patients with decompensated chronic liver disease (CLD), type 1 diabetes, patients with thyroid and adrenal dysfunction, patients taking drugs known to affect glycemic levels, acute or chronic malabsorption states, pregnancy or lactation were excluded from the study.

Cases were selected from gastroenterology clinic by non-probability consecutive sampling, provided they satisfied the selection criteria. The patients who were selected for the study were requested to provide informed written consent. Controls were chosen amongst those healthy-looking persons who reported for blood donation. All of them had anti-HCV antibodies tested by enzyme linked immunosorbent assay. Those with positive results were shifted to case group and had HCV RNA done by PCR. All the subjects finally selected for study got plasma glucose tested by hexokinase enzymatic method using Advia 1800 after at least an 8 hour fast.

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) version 23. All the numerical variables like age, duration of HCV infection, body mass index (BMI) and serum Alanine aminotransferase (ALT) were described as mean ± SD. Frequency and percentages were calculated for qualitative variables like gender, earlier treatment of chronic HCV and DM. Proportion of patients with DM was calculated for both groups and compared using chi-square test. The *p*-value of ≤0.05 was considered significant.

RESULTS

Patients in case and control groups had mean age of 40.26 ± 8.05 and 40.29 ± 8.89 years respectively whereas BMI in the case group was 26.60 ± 1.67 kg/m^2 and 26.05 ± 1.49 kg/m^2 in the control group. Mean duration of HCV infection was 7.03 ± 2.21 months in case group. Mean serum ALT levels was 46.81 ± 7.25 U/L in case group and 28.43 ± 4.66 U/L in control group (Table-I). A total of 76.8% of patients in case group had been treated for HCV infection previously (Table-II). Type 2 DM was seen in 38 (40%) cases and 19 (20%) controls (Odd Ratio=2.60; *p*=0.002) (Table-III).

Table-I: Characteristics of patients in both groups (n=190).

Demographics	Case Group n=95 Mean ± SD	Control Group n=95 Mean ± SD
Age (Years)	40.263 ± 8.05	40.294 ± 8.89
Body Mass Index (kg/m^2)	26.60 ± 1.67	26.052 ± 1.49
Duration of Hepatitis C Virus (months)	7.031 ± 2.21	-
Serum ALT levels (u/L)	46.81 ± 7.25	28.431 ± 4.66

Table-II: Patients with earlier treatment of HCV in case group.

Earlier treatment of Hepatitis C Virus	No. of Patients	Percentage
Yes	73	76.8%
No	22	23.2%

Table-III: Comparison of type 2 diabetes in both groups.

Type 2 Diabetes	Case Group n=95	Control Group n=95	Odd Ratio	*p*-value
Yes	38 (40%)	19 (20%)	2.60	0.002
No	57 (60%)	76 (80%)		

DISCUSSION

The association between DM and HCV infection has been suspected for decades.[11] Type 2 DM is a risk factor for CLD and 30% of patients with liver cirrhosis develop diabetes.[12] Diabetes and liver cirrhosis share couple of morphological changes such as deposition of glycogen in nucleus and cytoplasm as well as fat in liver cells, along with peri-sinusoidal fibrosis, are also present in liver cirrhosis.[13] This makes us believe that diabetes may be contributing to the associated liver disease. It has been proven that DM may rarely lead to liver cirrhosis, but more recently, DM was found to be implicated in the pathogenesis of liver cirrhosis through the progression of non-alcoholic steatohepatitis (NASH). Diabetes is seen in approximately 25-75% of people with NASH. Similarly, vast majority (90%) of those with NASH have been found to be over-weight/obese. In number of patients with DM, NASH progressing to liver cirrhosis has been documented.[14] The other established causes of CLD like chronic HCV infection may also coexist in diabetics and may lead to cirrhosis. CLD also affects the pathogenesis of diabetes. Liver plays an important role in carbohydrate metabolism. Thus, it is not surprising that 70% patients with cirrhosis have impaired glucose tolerance and relatively fewer patients develop overt DM.[15] Insulin resistance, hyperinsulinemia and hyperglucagonemia form the underlying basis of this abnormal glucose metabolism. The patients with advanced CLD are at risk to develop hyperglycemia even with usual doses of steroids or interferon.[16] Common causes of liver disease including alcohol, autoimmune conditions or hemochromatosis may co-exist and could be responsible for association of chronic liver disease with DM. Chronic hepatitis B and C are more frequently seen in patients with DM as compared to general population. In patients with DM frequent parenteral exposures may expose them to acquire HBV or HCV infections. There are number of studies suggesting the possible positive association between the chronic HCV infection and DM.[17] The study conducted by Gebrekristos *et al*,[15] manifested that out of 77 (16.7%) seroprevalence HCV, major proportion HCV was found among patients with DM being 64 (28%) versus 13 (6%) in other patients without DM. In another study, 200 patients recruited from UK for a prospective study revealed the higher incidence of chronic HCV infection among patients with DM. There is ample data from the developed countries to show increased prevalence of diabetes amongst patients with HCV associated CLD than liver diseases from other causes. Mason *et al*, published a case control study evaluating the relationship between DM and chronic HCV.[18] The cause-effect relationship was extensively studied, excluding every possible factor related to abnormal glucose handling. The authors found almost 1.75 times greater prevalence of DM in HCV-related CLD as compared to HBV infection. Moreover, diabetics had nearly three folds higher prevalence of chronic HCV infection as compared to controls. Same findings were noticed in advanced liver disease (unfit for transplant). The important question here is 'should DM be considered as the extrahepatic manifestations of chronic HCV infection?'. The aim of discussing this relationship is to assess the chances of acquiring HCV infection in diabetics as a result of frequent visits to health care facilities and venipunctures that occur in these patients. Moreover, as compared to HBV infection, HCV infection in adults has a very high transition rate of evolving into chronicity. Therefore, if the chances of exposure to two viruses are the same, chronic HCV infection prevalence is expected to be much higher than that for chronic HBV infection in the age matched population. The exact mechanism is not fully known, but might be related to viral replication at these extrahepatic sites leading to cytologic damage, immune mediated tissue damage or possible autoimmune processes induced by HCV. In this context, there is high possibility that chronic HCV infection may either activate latent autoimmunity in predisposed individuals or induce de novo an autoimmune disease through molecular mimicry and dysregulation of immune system. The immune dysregulation is supported by the association with thyroiditis, lichen planus and thrombocytopenia as well as the aggravation of these ailments with introduction of interferon therapy.[16]

Meta-analysis of various HBV studies have shown that 4% cases are carriers. Various population groups have about 32% prevalence of anti-HBs antibodies, indicating a natural seroconversion. However, these figures are of pre-vaccination era. Healthy population volunteers for blood donation having anti-HCV positivity rate varies from 1-4.4%. According to these figures, these two viruses are infecting Pakistani population at almost the same rate. Qureshi *et al*,[19] have reported a rather unusual finding of similar incidence of DM amongst patients with chronic infections secondary to HBV and HCV. The extrahepatic involvement of these two viruses is almost same because both viruses have the same exposure rate. Most of the above mentioned statistics for HBV infection are from pre or early HBV vaccination era. It will be interesting to re-evaluate these findings 2-3 decades after the HBV vac-

cination, when the chronic HBV infection prevalence is likely to fall, and see if this same prevalence of DM continues to persist in chronic HCV and HBV cases. Another study conducted by Villar *et al*,[20] concluded that low prevalence of HBV and high prevalence of HCV was observed in DM type 2 patients.

Frequency of DM is high among patients with HCV positive than HCV negative patients. Therefore, it is recommended that every patient who present with chronic HCV infection, should be evaluated for the presence of DM. However, it is also essential that all health care facilities should have their surveillance protocol in order to ascertain the exact frequency of the problem.

CONCLUSION

Type-2 diabetes mellitus is more frequent amongst HCV positive patients as compared to HCV negative patients.

Conflict of Interest: None.

Authors' Contribution

BR:, MA:, AJK:, ARA:, AA:, MR: Direct Contribution.

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