

# Frequency of Type 2 Diabetes Mellitus in Patients with Chronic Hepatitis C Virus Infection

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## ABSTRACT

**OBJECTIVE:** Type 2 Diabetes mellitus is more common among chronic hepatitis C patients. Various risk factors that predisposes chronic hepatitis C patients' to develop Type 2 Diabetes, includes age, sex, BMI and positive family history of diabetes mellitus. The objective of present study is to determine the frequency of Type 2 Diabetes mellitus in chronic hepatitis C virus infection and to compare the clinico-demographic features of hepatitis C cases with or without diabetes mellitus.

**METHODS:** This cross sectional study was done in medical wards of Liaquat University Hospital Hyderabad / Jamshoro from August 15, 2010 to February 15, 2011. Hundred consecutive patients of chronic hepatitis C virus infection were enrolled after getting informed consent. Baseline patient's data was collected with the help of a self-administered questionnaire which includes patient's history and physical examination. Patients were especially asked about family history of Diabetes mellitus and their body mass index (BMI) and blood pressure were recorded. Blood samples were drawn after twelve hours of fasting for fasting blood sugar and after two hours of taking meal for post prandial blood sugar. Liver function test, ultrasound abdomen and serological tests for hepatitis such as hepatitis B surface antigen (HBsAg) and anti hepatitis C antibody (antiHCV) were done in every patient. Patients with Type 1 Diabetes mellitus and those having positive results for both HBsAg and anti HCV antibody simultaneously were not included in the study. The data was analyzed by SPSS (statistical package for social science) version 10.0. For statistical data analysis, Chi square test was applied. A p value of < 0.05 was considered as statistically significant.

**RESULTS:** Hundred patients of chronic hepatitis C were included in the study. Sixty were males (60%) and forty (40%) were females. The age range of patients was 35-74 years and the mean age was 47.25± 11.02 (SD). Out of hundred patients, twenty seven (27%) had positive family history of diabetes mellitus and twenty eight (28%) had diabetes mellitus themselves. The BMI range of patients was 21-37 kg/m<sup>2</sup> and the mean BMI was 26.03kg/m<sup>2</sup> ± 4.30 (SD). Correlation of age (p = 0.001), BMI (p = 0.009) and family history of diabetes mellitus (p = 0.001) with the frequency of type 2 Diabetes mellitus in HCV +ve patients was statistically significant while comparison of gender with T2DM in HCV patient was not statistically significant (p = 0.413).

**CONCLUSION:** Type 2 Diabetes mellitus is more common among patients with chronic hepatitis C than those without hepatitis C. Increasing age, positive family history of diabetes mellitus and raised BMI are the risk factors for its development.

**KEY WORDS:** Frequency, Diabetes Mellitus, Hepatitis C.

## INTRODUCTION

Hepatitis C infection is a major cause of Chronic Liver Disease (CLD), affecting 3% of world's population<sup>1</sup>. Chronic hepatitis C infection is associated with an increased incidence of Type 2 diabetes mellitus (T2DM)<sup>2</sup>. T2DM is three times more prevalent among patients with chronic hepatitis C infection compared with other liver diseases and general population<sup>3</sup>. In Pakistan more than 10 million people are living with hepatitis C virus (HCV).<sup>4</sup> It is estimated that 3.3% of population globally (lower in Europe 1.03% and highest in Africa 5.3%) and 10% of Pakistani population is chronically

infected with this viral pathogen<sup>5,6</sup>. Genotype 3a is the most prevalent genotype in Pakistan affecting 50% followed by genotype 3b and 1a<sup>7,8</sup>. The sero prevalence of HCV is 6.7% in women and 1.3% in children in Pakistan<sup>9,10</sup>. Hepatitis C virus causes acute and chronic hepatitis and approximately 85% of HCV infections progress to chronicity<sup>11</sup>. HCV is now viewed as a true metabolic syndrome associated with T2DM, Hypertension, dyslipidemia, cardiovascular disease and atherosclerosis<sup>12</sup>. The most common modes of transmission of HCV in Pakistan are multiple use of syringes (61.45%), major or minor surgery or dental

procedure (10.62%), blood transfusions and blood products (4.26%), sharing razors during shaving and circumcision by barbers (3.90%), piercing instruments, nail clippers, tooth brushes, miswaks, needle stick injury (1%), from infected mother to baby and sexual transmission. The mode of transmission is unclear in about 20.35% subjects<sup>13, 14</sup>.

In 2005 an estimated 1.5 million (m) new cases of Diabetes Mellitus were diagnosed<sup>15</sup>. The center for disease control and prevention reported that the prevalence of Diabetes among people aged 20 years or older was 20.6 m (9.6% of the people in that age group) and the prevalence increased with age (10.3 m people aged 60 and above or 20.9% of those in that age group had diabetes)<sup>16</sup>.

Chronic HCV infection is associated with an increased risk of developing insulin resistance (IR) and T2DM. HCV seems to affect glucose metabolism via mechanisms that involve cellular pathways that have been implicated in the host innate immune response. IR and T2DM not only accelerate the histological and clinical progression of chronic hepatitis C infection but also reduce the early and sustained virological response to interferon based therapy. HCV may alter glucose homeostasis by its direct action, or via indirect mechanism such as through cytokine stimulation<sup>17</sup>. In patients with chronic HCV infection, direct interaction between HCV and insulin signaling components occur that may result in IR and T2DM in at risk individuals. Insulin stimulated IRS-1 tyrosine phosphorylation was decreased by 2 folds in HCV infected patients compared to non HCV infected ones, and this was paralleled by significant reduction in IRS-1/p85 phosphatidylinositol 3 (PI3)-kinase association, IRS-1 associated PI3-kinase activity and insulin stimulated Akt phosphorylation<sup>18</sup>.

Several mechanisms explain the link between HCV infection and T2DM. Chronic hepatitis C is associated with hepatic steatosis to a greater degree than other inflammatory diseases of liver. The insulin sensitivity is significantly decreased in chronic HCV infection<sup>19</sup>. It has been suggested that severe fibrosis is the only independent predictor of IR<sup>20</sup>. Tumor necrosis factor  $\alpha$  (TNF  $\alpha$ ) level is increased in human HCV infection and has an effect on insulin signaling<sup>18</sup>.

## METHODOLOGY

**Study Design:** This was a cross sectional study

**Study population and sample:** The study population consisted of patients of Chronic Hepatitis C. From this population, through convenience consecutive sampling, a sample of 100 patients selected to participate in this study, carried out at medical wards of Liaquat University Hospital, Jamshoro/Hyderabad from 15<sup>th</sup> Aug'2010-15<sup>th</sup> Feb' 2011.

**Inclusion and Exclusion criteria:** The following inclusion and exclusion criteria were used:

Only patients with chronic hepatitis C, both male and females, aged 35-74 years were included in the study. However, patients in whom Diabetes Mellitus was diagnosed before 30 and those having both hepatitis C and hepatitis B were excluded.

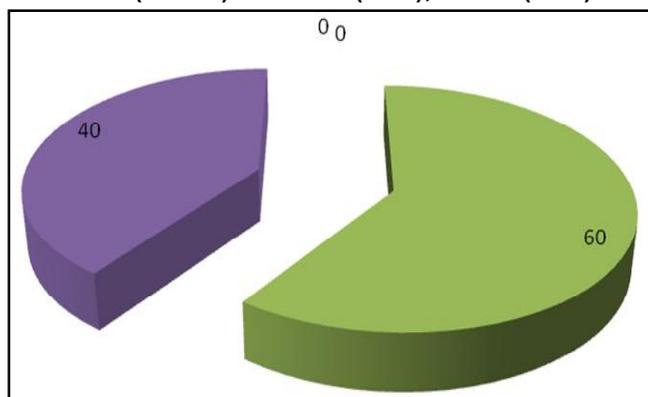
**Sampling Technique:** Patients who met the inclusion criteria were enrolled in the study. Baseline patient's data was collected via a questionnaire form including patient's history and physical examination. Patients were especially asked about family history of Diabetes mellitus and their body mass index (BMI) and blood pressure were recorded. Blood samples (3 ml in fluoride tubes) were drawn after 12 hours fast and 2-hour post prandial for fasting and random blood sugar respectively. The samples were transported to research and diagnostic laboratory of Liaquat University of Medical and Health Sciences Jamshoro within half an hour of collection. The method used was "PAP" enzymatic calorimetric test. Serological tests for hepatitis (HBsAg, anti HCV), LFT and ultrasound abdomen was done in every patient. The data was analyzed by SPSS (statistical package for social science) version 10.0. Chi square test or Z-test of proportion was used for comparison of qualitative output response. Mean Standard deviation (SD) and standard error of mean (SEM)  $\pm$  was calculated. A p value of  $< 0.05$  is considered as statistically significant.

## RESULTS

A total of 100 patients of chronic hepatitis C were included in the study. Out of 100 patients, sixty were males (60%) and forty (40%) were females. Graph I shows the sex distribution of the patients. The frequency of diabetes mellitus among hepatitis C patients was 28%. Table I shows the frequency of T2DM in HCV +ve patients. The mean age of patients was  $47.25 \pm 11.02$  (SD) with the range of 35-74 years. Majority of patients studied were between 35-44 years (52%). Among 100 cases, family history for Diabetes Mellitus was positive in 27 patients only. Of the 28 diabetic patients, 18 (68.28%) were over 45 years of age. Table II shows the age distribution of patients. Out of 28 diabetic patients, 15 (53.57%) had positive family history of Diabetes Mellitus ( $p = 0.001$ ). Table III shows the family history of Diabetes Mellitus. The mean BMI was  $26.03 \pm 4.31$  (SD) with the range of 21-37 kg/m<sup>2</sup>. Out of 100 patients, only 52 (52%) had BMI less than 25 kg/m<sup>2</sup>. Of the 28 diabetics, only 7 had BMI less than 25 kg/m<sup>2</sup> while 21 had BMI more than 25 ( $p = 0.009$ ). Table IV shows the BMI of the patients. Correlation of age ( $p = 0.001$ ), BMI ( $p = 0.009$ ) and family history of diabetes mellitus ( $p =$

0.001) with the frequency of type 2 Diabetes mellitus in HCV +ve patients was statistically significant while comparison of gender with T2DM in HCV patient was not statistically significant ( $p = 0.413$ ). Table V shows the statistical comparison of frequency of Diabetes Mellitus with age, sex, positive family history of Diabetes and BMI.

**GRAPH I: SEX DISTRIBUTION OF PATIENTS STUDIED (N=100) FEMALE (40%), MALE (60%)**



**TABLE I: FREQUENCY OF T2DM IN HCV POSITIVE PATIENTS (n=100)**

|               | Frequency  | Percentage |
|---------------|------------|------------|
| T2DM          | 28         | 28         |
| Non-Diabetics | 72         | 72         |
| <b>Total</b>  | <b>100</b> | <b>100</b> |

**TABLE II: AGE DISTRIBUTION OF PATIENTS STUDIED (n=100)**

| <b>(a) Age Distribution: Mean and SD</b>              |            |            |
|---|------------|------------|
| Mean  | 47.25      |            |
| Range   | 35-74      |            |
| Standard Error of Mean                                | 1.10       |            |
| Standard Deviation                                    | 11.02      |            |
| <b>(b) Age Distribution: Frequency and Percentage</b> |            |            |
| Age   | Frequency  | Percentage |
| 35-44   | 52         | 52         |
| 45-54   | 22         | 22         |
| 55-64   | 11         | 11         |
| 65-74   | 15         | 15         |
| <b>Total</b>  | <b>100</b> | <b>100</b> |

**TABLE III: FAMILY HISTORY OF DIABETES MELLITUS (n=100)**

| Family History   | Frequency  | Percentage |
|------------------|------------|------------|
| Positive History | 27         | 27         |
| Negative History | 73         | 73         |
| <b>Total</b>     | <b>100</b> | <b>100</b> |

**TABLE IV: BODY MASS INDEX (BMI) OF SUBJECTS (n=100)**

| <b>(a) BMI: Mean and SD</b>              |            |            |
|--|------------|------------|
| Mean                                     | 26.0300    |            |
| Range                                    | 21-37      |            |
| Standard Error of Mean                   | 0.4308     |            |
| Standard Deviation                       | 4.3075     |            |
| <b>(b) BMI: Frequency and Percentage</b> |            |            |
| BMI (Kg/m <sup>2</sup> )                 | Frequency  | Percentage |
| Less than 25                             | 52         | 52         |
| 25-29.9                                  | 25         | 25         |
| 30-34.9                                  | 17         | 17         |
| More than 35                             | 6          | 6          |
| <b>Total</b>                             | <b>100</b> | <b>100</b> |

**TABLE V: STATISTICAL COMPARISON OF FREQUENCY OF DIABETES MELLITUS WITH AGE, SEX, FAMILY HISTORY AND BODY MASS INDEX**

| Parameters                 | Chi Square Value | Degree of Freedom (df) | P Value |
|----------------------------|------------------|------------------------|---------|
| Age (Years)                | 60.152           | 31                     | 0.001   |
| Sex                        | 0.67             | 1                      | 0.413   |
| Family History of Diabetes | 10.437           | 1                      | 0.001   |
| BMI (Kg/m <sup>2</sup> )   | 11.531           | 3                      | 0.009   |

**DISCUSSION**

Chronic Hepatitis C and Diabetes mellitus cause devastating long term complications in a significant minority of patients. A link between the two disorders would not be surprising. Chronic Hepatitis C infection can cause cirrhosis, which, through IR, predisposes the patient to Diabetes Mellitus. Recent cross sectional studies performed worldwide suggest that they are indeed closely linked<sup>21</sup>. Many of previous investigations have documented an

association between HCV infection and T2DM. Present study, also supports detection of increased risk for T2DM among HCV patients as more than quarter of Chronic Hepatitis C patients had Diabetes. A study conducted at Karachi by Qureshi et al shows that 24.5 percent of HCV positive patients had Diabetes Mellitus<sup>22</sup>. Another study conducted in Islamabad shows that 18 percent cases of HCV infection have Diabetes Mellitus<sup>23</sup>. The results of current study also correlates with other studies conducted in different parts of the world like China 19.05percent<sup>24</sup>, Italy 32.5percent<sup>25</sup>, Los Angeles 21percent<sup>26</sup>, Israel 86.33percent<sup>27</sup> and Korea 24percent<sup>28</sup>. Allison and co-workers found that among patients with cirrhosis awaiting transplantation, those who were infected with HCV were 5 times more likely to have T2DM than those who were not, regardless of sex, BMI or severity of liver disease<sup>29</sup>.

Our study shows that increasing age is a risk factor for T2DM in HCV infected patients as 68.2 percent patients who had Diabetes Mellitus were over 45 years of age. The study of Mitchell et al and Shurti et al shows that patients with old age are at high risk to develop Diabetes Mellitus than those who were younger<sup>30, 31</sup> and our findings are in agreement with it. Positive family history of Diabetes Mellitus is a risk factor for the development of T2DM in chronic Hepatitis C patients and present study proves the same as more than half of diabetic patients had positive family history of Diabetes Mellitus. The results correlates with another study conducted by Samir et al that shows that 41.08 percent had positive family history of Diabetes Mellitus and the prevalence of Diabetes Mellitus was significantly increased in subjects with HCV infection compared to those with HBV infection 56.5 percent against 2.7 percent<sup>32</sup>.

Obesity has been shown to be among the most important risk factors for T2DM. In our study, only quarter of diabetic patients had BMI less than 25 kg/m<sup>2</sup>. Other studies also show the same relation of obesity with Diabetes Mellitus<sup>33, 34</sup>. Another study shows that approximately 20percent of patients with HCV infection were obese and that obesity in those individuals was associated with steatosis and progression of fibrosis<sup>35</sup>. Nevita et al reported that BMI was associated with increased risk of Diabetes Mellitus in patients with HCV genotype 1 and 2 and who had no family history of Diabetes Mellitus<sup>36</sup>.

## CONCLUSION

Type 2 Diabetes Mellitus occur frequently in patients with chronic Hepatitis C infection and growing age, positive family history of diabetes mellitus and increased BMI make these patients more prone to develop DM.

## RECOMMENDATION

Large prospective studies should be carried out to include persons at high risk for both HCV and Diabetes Mellitus to establish firm relationship between HCV and T2DM and to assess biological mechanisms.

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