

Prevalence of Diabetes Mellitus in Subjects with Chronic Hepatitis C Infection

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Hepatitis C virus (HCV) infection and type 2 diabetes mellitus (T2DM) are two major public health problems associated with increasing complications and mortality rates worldwide. HCV infection and T2DM may coexist in an individual. HCV infected individuals have a greater chance of developing insulin resistance (IR) and diabetes (DM). Moreover, HCV patients with IR, with or without diabetes, have a poor response to antiviral treatment, increased progression of liver fibrosis and greater risk of developing hepatocellular carcinoma. Objectives of this study were to find out the estimated prevalence of diabetes mellitus in subjects with chronic hepatitis C infection and to find out the association between chronic HCV infection with other related features of diabetes such as age, gender, family history of diabetes and body mass index. A cross-sectional descriptive study was done in total 130 HCV-positive subjects from December 2016 to June 2017. Plasma glucose test, HbA1c test and liver function test were done. In this study, males were 56 (43.1%) and females were 74 (56.9%). Out of 130 subjects, 5 subjects (3.8%) were diagnosed as DM, where 63 subjects (48.5%) and 62 subjects (47.7%) were diagnosed as pre-diabetes and normal blood glucose level, respectively. In this study, the prevalence of DM case was low and the prevalence of pre-DM was relatively higher. In conclusion, early diagnosis of DM in HCV-positive subjects can give early treatment and better management of DM. Well control glycemic status in HCV-positive subjects will give slow progression of liver fibrosis and better response of antiviral treatment. This study also provided the awareness of pre-DM and early prevention of DM in pre-DM subjects by changing the healthy life styles.

Keywords: Chronic hepatitis C infection, Diabetes mellitus, Pre-diabetes, Insulin resistance

INTRODUCTION

Hepatitis C virus (HCV) infection and type 2 diabetes mellitus (T2DM) are two major public health problems associated with increasing complications and mortality rates worldwide.¹ Data reported by the World Health Organization (WHO) in 2000 showed that the estimated prevalence of T2DM is approximately 2.8% among adults aged over 20 years.² Report on national survey of diabetes mellitus and risk factors for non-

communicable disease in Myanmar, 2014 showed that prevalence of DM in Myanmar was 10.5%, and prevalence of DM in Yangon Region was higher in 2014 (18%) than in 2003 (12%).³ Both diseases present a large health care burden. Moreover, HCV infection and T2DM may coexist in an individual.⁴ Previous research suggests a link between diabetes and

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chronic HCV, HCV infected individuals, have a greater chance of developing insulin resistance (IR) and diabetes. Moreover, HCV patients with IR with or without diabetes, have a poor response to antiviral treatment, increased progression of liver fibrosis and greater risk of developing hepatocellular carcinoma.⁵

The prevalence of diabetes mellitus (DM) had been reported in 21% to 50% 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.⁶ The prevalence of DM in HCV patients was 31.5% in Pakistan population.⁷

HCV infection induces an immune response characteristically mediated by Th1-cells. These lymphocytes secrete γ interferon as the predominant cytokine, which is able to enhance the production of TNF- α by macrophages. At the same time, HCV directly causes liver fat deposition. All these events could be potential risk factors for liver fibrosis. Liver fibrosis, TNF system, and liver steatosis are also associated with the development of IR and T2DM. Alternatively, hyperinsulinemia can adversely affect the course of liver fibrosis through both the proliferation of stellate cells, thus enhancing the secretion of extracellular matrix, and the expression of the connective tissue growth factor (CTGF).⁸

The prevalence of HCV infection in patients with T2DM are more common than the general population, which was considered to be the result of more frequent exposure to medical interventions and instrumentation and compromised immunity, leading to an increased risk of HCV infection.⁹ In Myanmar, a hospital-based cross-sectional study was done at Yangon General Hospital and New Yangon General Hospital in 2007. This study showed that the prevalence of HCV infection in DM was 19% (19/100), and concluded that HCV infection occurs more often in T2DM and further investigation for HCV infection should be done in DM patients with raised ALT.¹⁰

HCV replication may be favored by hyperinsulinemia and/or the increased serum levels of free fatty acids observed in patients with IR and T2DM.¹¹ Additionally, T2DM is, to some extent, associated with an immunocompromised state, which leads to derangements of immune function.¹² Both IR and T2DM may play a role in the alteration of the natural course of HCV infection, thus leading to be enhanced steatosis, steatohepatitis, and liver fibrosis.¹³

Increasing levels of IR are associated with reduced rates of virological response in chronic hepatitis C patients treated with a combination of pegylated IFN- α and ribavirin. This negative association has been reported not only in HCV genotype 1 but also in genotypes 2 and 3.⁶

The treatment of IR and T2DM in chronic hepatitis C patients has aimed to reduce fibrogenesis and to increase the response to IFN-based therapy. Lifestyle changes (weight reduction and increased physical activity) should constitute the clinical management of patients with chronic hepatitis C and initial glucose metabolism derangements, with the aim of reducing their progression to overt T2DM and possibly, their impact on liver fibrogenesis. IR should be corrected in patients with chronic hepatitis C not responding to IFN- α -based treatment, in order to improve response upon retreatment.⁶

HCV infection and T2DM are two common disorders with a high impact on health worldwide. A high prevalence of T2DM among HCV infected patients with chronic hepatitis has been consistently reported, and there is growing evidence to support the concept that HCV infection is a risk factor for developing T2DM.⁸ This study was important as it determined the prevalence of DM in subjects with chronic hepatitis C infection. Early diagnosis of DM in HCV-positive subjects could give early treatment and better management of DM. Well control glycemic status in HCV-positive subjects would give slow progression of liver fibrosis and better response of antiviral treatment.

MATERIALS AND METHODS

It was a cross-sectional descriptive study conducted at the Hepatitis Carrier Clinic, Department of Medical Research (DMR) and the Out-patient Department of Liver Medical Unit, Yangon Speciality Hospital (YSH). A total 130 chronic hepatitis C infected subjects at age of 18 years and above were recruited at Hepatitis Carrier Clinic (DMR) and OPD (YSH) from December 2016 to June 2017.

Pregnant women, patients with concomitant HCV and HBV infections, known history of type 1 diabetes mellitus, history of alcohol abuse, history of regular taking corticosteroid or hydrochlorothiazide, known or suspected case of haemochromatosis or autoimmune disease, known history of pancreatitis or pancreatic tumor, complication of chronic hepatitis infection such as cirrhosis and hepatocellular carcinoma were excluded in this study.

Procedure of the study

All the selected subjects were explained about the study and obtained the written informed consent. History taking, weight and height measurement (BMI calculation) were done according to proforma. Under aseptic condition, 2 ml of venous blood samples were collected from antecubital vein for random plasma glucose test, HbA1c test and liver function test. The subjects who needed to do fasting plasma glucose test were explained about fasting (no caloric intake ≥ 8 hrs), and the test was done on next day. The plasma glucose level was measured by using chemical analyzer within 24 hours and HbA1c test was done by NycoCard READER II (Boronate affinity test principle).

Criteria for diagnosis of diabetes¹⁴

1. In persons with symptoms of hyperglycemia* or hyperglycemic crisis*,
 - Random plasma glucose ≥ 200 mg/dl (11.1 mmol/l) (or)
 - Fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l) (or)
 - HbA1C $\geq 6.5\%$ (48 mmol/mol)

2. In persons without symptoms of hyperglycemia or hyperglycemic crisis, diagnosis should not be based on a single test. At least one additional test on another day requires for confirmation.

3. Known cases of diabetic patients who had already taken oral hypoglycemic drug.

*Hyperglycemic symptoms are frequent urination, increased thirst, blurred vision, fatigue and headache.

*Hyperglycemic crisis symptoms are fruity-smelling breath, nausea and vomiting, shortness of breath, dry mouth, weakness, confusion, coma and abdominal pain.

Data analysis

Data analysis was done by SPSS (version 16). Prevalence and associated factors of diabetes in HCV patients were evaluated in frequency and percentage. The mean values of age, BMI, RBS, HbA1C, ALT and AST among three groups were compared using ANOVA test. Statistical significance was set at $p=0.05$.

Ethical consideration

The research proposal was submitted to the Ethics Review Committee, Department of Medical Research. The subjects were informed about the objective and details of the procedure of the study before getting consent and have the right to refuse for this research study if they do not want to participate without any disturbance in getting their medical care. The patients were informed and explained about test result and referred for proper management in necessary cases.

RESULTS

The mean age of the study population (\pm standard deviation) was 50.4 ± 12.1 with a range of 22-80 years of age. Male and female populations were 43.1% and 56.9%. The majority of the study populations were married (78.46%) as compared to the single ones (21.54%). Overall prevalence of type 2 diabetes mellitus was 3.8% (5/130) and non-diabetes was 96.15% (125/130). Among non-diabetes, pre-diabetes was 63/125 (48.5%) (Table 1).

Table 1. Prevalence of diabetes, prediabetes and normal group in HCV seropositive subjects

	HCV patients	
	Number	Percent
Diabetes	5	3.8
Pre-diabetes	63	48.5
Normal group	62	47.7
Total	130	100

Table 2 shows comparison of means between diabetes, prediabetes and normal glucose of HCV-seropositive subjects. There is no significant association between these three groups and mean values of age, BMI, ALT, AST level.

Table 2. General characteristics of diabetes, prediabetes and normal group in HCV seropositive subjects

Mean±SD	Diabetes	Pre-diabetes	Normal group	P value
	N	N	N	
Age	52.0 ±12.0	52.0 ±12.2	48.5 ±12	0.260
BMI	25.32 ±3.4	23.6 ±3.9	22.9 ±3.7	0.308
Random blood sugar (mg/dl)	206.0 ±54	100.4 ±19.7	97.3 ±19.3	<0.001
HbA1c (%)	8.1 ±2.7	6.1 ±0.3	5.3 ±0.7	<0.001
ALT (1U/L)	73 ±36.6	47.7 ±26.0	45.7 ±35	0.200
AST (1U/L)	61.8 ±34.7	43.9 ±19.4	52.9 ±44.7	0.436

As shown in Table 3, diabetes and prediabetes were mostly found in the 65 and above age group and normal glucose was mostly found in 18-44 years age group. From gender aspect, females were more susceptible to get diabetes, 5.4%, whereas males were 1.8%. More proportion of patients with BMI \geq 25 group (10.8%) was found having DM than BMI <25 group (1.1%). Among patients with family history, 8.7% were diabetes but only 2.8% of those without family history were diabetes in this study. In addition, the longer period of HCV infection (>5 yrs) showed the more prone to have diabetes (9.1%) compared with the shorter duration (<5 yrs) which reported only 2.8%.

However, there was not statistically significant association between risk factors and diabetes in HCV patients in this study.

Table 3. Associated factors between diabetes, prediabetes and normal glucose in HCV seropositive subjects

Associated factors	Chronic hepatitis C infection			
	Diabetes	Pre-diabetes	Normal group	Total (N=130)
	N (%)	N (%)	N (%)	N (%)
<i>Subjects</i>	5(3.8)	63(48.5)	62(47.7)	130(100.0)
<i>Age</i>				
18-44	1(2.7)	17(45.9)	19(51.4)	37(100.0)
45-64	3(4.0)	34(45.3)	38(50.7)	75(100.0)
65 and above	1(5.6)	12(66.7)	5(27.8)	18(100.0)
<i>Gender</i>				
Male	1(1.8)	30(53.6)	25(44.6)	56(100.0)
Female	4(5.4)	33(44.6)	37(50.0)	74(100.0)
<i>Body mass index</i>				
<25	1(1.1)	45(48.4)	47(50.5)	93(100.0)
\geq 25	4(10.8)	18(48.6)	15(40.5)	37(100.0)
<i>Family history of DM</i>				
Yes	2(8.7)	11(47.8)	10(43.5)	23(100.0)
No	3(2.8)	52(48.6)	52(48.6)	107(100.0)
<i>Duration of HCV Infection</i>				
<5 yrs	3(2.8)	50(46.3)	55 (50.9)	108(100.0)
>5 yrs	2(9.1)	13(59.1)	7(31.8)	22(100.0)

DISCUSSION

In this study, the prevalence of diabetes in HCV-seropositive subjects was 3.8%. The lower rate of diabetes was observed in this study (3.8%) as compared to non-infected Myanmar population (10.5%).³ The prevalence of T2DM in HCV infected patients in Pakistan, 2014-2015, was 26.42%.¹⁵ One of the explanations was that sample size in this study (n=130) was very small as compared with Myanmar national survey in 2014 (n=8,757).³ Another reason was that HCV-seropositive subjects in this study were both already anti-HCV treatment taken and newly diagnosed. If HCV treatment was already taken and viral clearance present, pathophysiological mechanism of HCV infection to insulin resistance and diabetes was not occurring anymore in those patients.

Arase *et al.*,¹⁶ also reported a decreased incidence of diabetes after successful treatment of HCV (sustained virological response; SVR).

The study of Imazeki *et al.* showed that the prevalence of DM in the HBV chronic, HCV chronic and HCV cleared groups were 6.3, 13.6 and 9.0%, respectively, and the prevalence of IR in the HCV+ chronic group (54.3%) was also higher than that in the HBV+ chronic (36.3%) ($p < 0.005$) and HCV+ cleared groups (35.7%) ($p < 0.05$).¹⁷

The relationship of hepatitis C virus infection with diabetes in the U.S population stated that the overall prevalence of diabetes in hepatitis C patients was 10.5% and prediabetes was 32.8%, and also concluded that HCV infection was not associated with diabetes.¹⁸ A Southern Italy cohort study at population level also stated no association between incident cases of diabetes and positive anti-HCV antibodies.¹⁹

In the present study, the prevalence of prediabetes in HCV seropositive subjects (48.5%) was a twice higher than general population (20%) in Myanmar.³ One Egyptian study agreed that prediabetes was significantly higher among HCV group compared with the control group.²⁰ Narita *et al.*²¹ study was in agreement with that glucose tolerance was detected in 27.5% (36/131) of chronic hepatitis C patients in which 10 had diabetes and 26 impaired glucose tolerances (prediabetes). It was observed in this study that positive cases of diabetes and prediabetes with respect to age ($p = 0.26$), gender ($p = 0.4$) and body mass index (BMI) ($p = 0.308$) had insignificant relationship. Studies from Italy and USA referred that HCV increases the prevalence of DM independently of age.^{22, 23}

The mean age for HCV diabetes and prediabetes was higher than the mean age for HCV glucose normal subjects which was interestingly similar to the findings of Elhawary *et al.*²⁴ These findings support the idea that the induction of diabetes in HCV patients is progressive rather than abrupt.²⁵ In this study, most of diabetes were among age group of

45-64 years (4%) and ≥ 65 years (5.6%). Elhawary *et al.* reported that the highest percentage of diabetes (37.5%) was among age group of 41-50 years.²⁴ Centers of Disease Control and Prevention (CDC) also described that adults aged 45 to 64 were the most diagnosed age group for diabetes in 2012.²⁶

HCV infected males (56/130) and females (74/130) were participated in this study. Diabetes was more prevalent in females (5.4%) than in males (1.8%). However, in an Egyptian study, diabetic HCV males and females were 72.5% and 27.5%, respectively.²⁴ In this study, 10.8% of patients with BMI more than 25 have diabetes. One Southern Italy study found an association between HCV and diabetes only in subjects who were older, overweight and of low-socioeconomic status.¹⁹ In this study, 9.1% and 59.1% of patients with HCV infection duration more than 5 years are diabetics and prediabetics, and 50.9% of patients with HCV infection duration less than 5 years were normal. They might have enough duration for HCV virus to give clinical consequences of insulin resistance and diabetes.

In this study, mean values of ALT in diabetes (73 ± 36.6) and prediabetes (47.7 ± 26.0) were higher than those of normal glucose subjects (45.7 ± 35), but not strongly associated. Montenegro *et al.*¹⁹ stated that an increased ALT was strongly associated with diabetes regardless of HCV antibodies status. The increased ALT values may be due to either HCV or conditions such as metabolic syndrome or steatohepatitis independently from HCV, conditions that could cause insulin resistance and then diabetes.¹⁹ As positive family history was already major contribution factor of diabetes, among patients with family history, 8.7% were diabetics but only 2.8% of those without family history were diabetics in this study.

Limitation of study

There were certain limitations of this study. The most important limitation in this study was small sample size, and included HCV-seropositive subjects were already taken anti-HCV treatment.

Conclusion and recommendation

This study concluded that there was increased prevalence of prediabetes in HCV seropositive subjects and no significant association between risk factors of diabetes such as age, gender, BMI and family history of diabetes. It highlighted that there might be the links between HCV infection and diabetes. It recommends that the effect of insulin resistance on chronic hepatitis C patients should be evaluated in a larger sample size.

Competing interests

The authors declare that they have no competing interests.

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