

Hepatitis C Virus Infection in Diabetes Mellitus Patients

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ABSTRACT

Introduction: Chronic hepatitis C virus (HCV) infection and type 2 diabetes mellitus cause long-term complications in affected patients. Moreover, both disorders are common. Recent cross-sectional studies performed worldwide suggest that they are indeed closely linked. Diabetic patients are at an increased risk of acquiring (HCV) infection because of the nature of the disease and its complications or frequent parenteral exposure. On the other hand Hepatitis C infection may itself contribute to the development of Diabetes Mellitus. The epidemiological evidence of this association has not been studied in Myanmar.

Objective: It was to study the frequency of HCV infection among adult diabetic patients attending the diabetic clinic of a hospital in Myanmar.

Method: The study is a hospital based cross sectional study, comprised of 100 diabetic patients visiting the diabetic clinic of Yangon General Hospital, in Myanmar. Subjects were previously confirmed diabetes cases or newly diagnosed diabetes according to World Health Organization criteria. The presence of (HCV) infection was tested by SERODIA-HCV Gelatin Particle Agglutination Test method at the National Health Laboratory of Union of Myanmar. A concise history of the patient, examination and laboratory findings were recorded on a proforma.

Result: Out of 100 diabetics, 19 were found to be anti-HCV positive and all of them had type 2 diabetes mellitus. There was no gender difference in the seropositive cases. Serum alanine aminotransferase (ALT) level was raised in 73.7% of the positive cases as compared to the 18.5% of the seronegative patients. Hepatomegaly was found in 68.4% in seropositive cases in contrast to 18.5% of seronegative cases.

Conclusion: (HCV) infection occurs more often in type 2 diabetics and further investigations should be done in diabetic patients with raised ALT for the presence of chronic (HCV) infection.

Keywords: Diabetes Mellitus, Hepatitis C virus Infection, Alanine aminotransferase, Hepatomegaly, Myanmar

Introduction

The awareness of viral hepatitis has increased over the past few decades. Hepatitis C virus (HCV) infection is a common cause of acute and chronic hepatitis, and leads to cirrhosis and hepatocellular carcinoma. It is estimated that nearly 150 to 200 million people have been in contact with HCV worldwide, and approximately 85% have chronic infection. Recent cross-sectional and longitudinal studies have shown that chronic HCV infection is associated with a higher risk of developing insulin resistance (IR) and type 2 diabetes mellitus (T2DM)¹.

Several controlled studies have found a significant association between these two conditions, HCV-positive rate among diabetics being two to seven fold compared to controls^{2,3,4}. Similar findings of increased prevalence of HCV infection among diabetics are also noted in some uncontrolled studies^{5,6}. Hui and collaborators have discovered that HCV seropositive rate among patients with type 2 diabetes mellitus is more than that in the general population, a finding consistent for different ethnic groups⁷. Furthermore, most of the anti-HCV positive diabetic patients presented with abnormal liver function tests⁸.

Similarly, diabetes mellitus is reported to be more prevalent in patients with chronic hepatitis C than in patients with other liver diseases, in the absence of predisposing factors. These findings suggest a role of HCV infection in the pathogenesis of diabetes⁹.

The estimated prevalence of diabetes mellitus in Myanmar was 2.5% in 2000. The overall prevalence of anti-HCV was 2.6% in 2002, 1.6% in 2003, 0.80% in 2004, 0.66% in 2005 and 0.75% in 2006 respectively¹⁰.

Although these two diseases are prevalent in Myanmar, there have been no studies to find out the association between them. This study aims to evaluate the prevalence of hepatitis C virus (HCV) infection, clinical and biochemical status of liver function in diabetes mellitus patients among a group of Myanmar people.

Aim

To study HCV infection in diabetes mellitus patients attending diabetic clinic at Yangon General Hospital, Myanmar

Objectives

- a. To study the demographic and background characteristics of both HCV positive and HCV negative diabetic patients
- b. To find out the biochemical parameters of liver function status and imaging profile in both HCV positive and HCV negative diabetic patients

Material and Method

This study was a hospital based cross sectional descriptive study conducted at the diabetic clinic of Yangon General Hospital between 1st March 2006 and 28th February 2007. Subjects for the study were selected according to simple random sampling method who meets the selection criteria. The inclusion criteria were: a) the confirmed diabetic patients and b) newly diagnosed diabetic patients by WHO criteria (1999). The exclusion criteria were history of alcohol taking in the last 1 year, history of taking hepatotoxic drugs, evidence of acute clinical hepatitis and those who are HBsAg positive.

After consents were obtained, thorough history was taken for sociodemographic data (age, sex, and race) and background characteristics of diabetes (family history of diabetes, duration and type of diabetes mellitus, mode of anti-diabetic therapy).

The presence of HCV infection was carried out by SERODIA-HCV Gelatin Particle Agglutination Test method using gelatin particle carriers sensitized with recombinant antigens c22-3 and c200 at the National Health Laboratory of Union of Myanmar. Weight, height and Body Mass Index (BMI) were measured using standard procedures. Serum bilirubin, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase, γ glutamyl transferase (GGT), Prothrombin Time (PT) were performed by 550 Expressed Plus Automatic Chemistry Analyzer at the Pathology Department of Yangon General Hospital for biochemical assessment of liver function. USG examination of abdomen was carried out by the same radiologist at the Radiology Department of Yangon General Hospital to determine the size and echogenicity of the liver, as well as the evidence of space occupying lesion in the liver. All collected data was recorded and analyzed using SPSS software for windows version 10.0.

Results

Out of the total 100 diabetic subjects studied, 19 (19%) turned out to be anti-HCV positive, All of these 19 subjects (100%) had type 2 diabetes. Among them, 9 subjects (47.4%) were male and 10 subjects (52.6%) were female.

On observing the age groups of anti-HCV positive diabetic patients, it was noticed that 1 subject (5.3%) was in the 20-39 years range, 13 subjects (68.4%) in the 40-59 years range, 5 subjects

(26.3%) were above 60 years of age. Mean age of diabetic patients with HCV infection was 55.3 ± 10.7 years and that of seronegative diabetic patients was $56.9 \text{ yr} \pm 9.1$ years.

Biochemical markers of liver function were found to be significantly higher in seropositive cases than seronegative patients. (Table 1)

Hepatomegaly was significantly associated with HCV infection but echogenicity and SOL have no significant relation with it. (Table 2)

Discussion

In our study we found that almost one fifth of diabetics were Anti-HCV positive.

The association of diabetes mellitus with chronic liver disease has been recognized many years ago. Russian endocrinologists reported abnormalities of glucose tolerance in 28% of patients with chronic liver disease in 1977¹¹. The increased frequency has been supported in many other studies. Simo et al, in 1996 found that HCV infection in diabetic patients was 4.39 times higher compared to the control group⁸. Similarly, a study in Pakistan reported a higher frequency of HCV infection, particularly genotype 2a, among diabetic patients¹².

All the seropositive cases in this study were type 2 diabetics. This finding of stronger association with type 2 diabetics is seen in many other studies¹³. Gray H. et al. suggested the possible association between HCV infection and type 2 diabetes mellitus, especially in Afro-Caribbean population⁵. Similarly Caronia et al have confirmed the relationship between type 2 Diabetes and HCV infection¹⁴.

Most of the seropositive diabetics in this study were in the 5th or 6th decade of their lives. This is in accordance with a national survey in United States which showed that HCV infection in type 2 diabetes mellitus occurred more frequently in patients older than age 40¹³. In another United States study advanced age was similarly pointed as one of the most frequent risk factors for the presence of clinical and biological extra hepatic manifestations of chronic HCV¹⁵.

We could not detect any relationship between gender and presence of seropositivity in this study. According to Caronia et-al, male sex was one of the major factors associated with type 2 diabetes mellitus¹⁴. However, Cacoub. P et-al reported female sex as one of the most frequent factors for the occurrence of extra hepatic manifestations of HCV infection¹⁵.

The study does not reveal significant association between duration of diabetes and hepatitis C seropositivity. This shows that chronicity of diabetes mellitus is not a predisposing factor for HCV infection. It may be the hepatitis C infection itself leading to the development of diabetes through an uncertain mechanism.

We found elevated liver enzymes, especially ALT has a direct relationship with seropositivity in the diabetic population, showing the relevance of this as a screening test in diabetics. Many researchers have highlighted this importance. In a study by Mason et al, more than 20% of

diabetes patients with consistently elevated serum aminotransferases had evidence of HCV infection¹⁶. Simo and colleagues similarly discovered that most of the anti-HCV positive diabetic patients (72.2%) presented with an abnormal liver function tests, a combination of hepatocellular and cholestasis pattern being the predominant biochemical alteration⁸. A study from United States revealed a consistently elevated serum aminotransferases in 32% of the HCV-infected diabetics compared with 5% of those without infection¹⁶.

Elevation of ALT in hepatitis C positive diabetes patients in this study is usually mild, with most having ALT level between one to two times upper limit of normal.

This study also shows a strong and significant relation between presence of HCV infection and hepatomegaly but not with liver echogenicity or the presence of space occupying lesion in the liver.

Based on the findings of this study, elevated liver enzymes and/or hepatomegaly in a diabetic patient should not be ignored as it may be due to fatty infiltration of the liver caused by underlying diabetes or insulin resistance, even if the elevation may be mild. Therefore, our study points out the need to test for hepatitis C virus infection in any diabetic patient with elevated liver enzymes and/or hepatomegaly.

Conclusion

Based on the findings in our study, there exists a positive relationship between HCV infection and type 2 diabetes mellitus and these hepatitis C infected diabetic patients have significantly higher rate of abnormal liver function tests. Elevation of ALT is usually between one to two times upper limit of normal in seropositive patients. Furthermore, we also found that seropositive diabetic patients have significantly higher rate of hepatomegaly with no significant relation with echogenicity or space occupying lesion in liver on ultrasonographic examination. Therefore we can conclude that abnormal liver function tests in hepatitis C infected diabetic patients are not attributable to underlying cirrhosis or hepatocellular carcinoma. Based on our data, we believe that the presence of raised Alanine Amino Transaminase (ALT) levels in diabetic subjects should be considered as an indication for further investigations. In conclusion, a diabetic patient with abnormal liver function test and/or hepatomegaly should not be ascribed merely to fatty infiltration of the liver. Screening for hepatitis C infection is highly advisable in such patients. We strongly recommend further studies on genotyping of hepatitis C virus in future research to identify the specific genotype of hepatitis C virus associated with diabetic population in Myanmar.

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Conflict of Interest: None declared.

References

1. Negro F, Alaei M: Hepatitis C virus and type 2 diabetes. *World J Gastroenterol.* 2009; 15(13): 1537-1547.
2. Mason AL, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology.* 1999; 29: 328-333.
3. Okan V, et al. Increased frequency of HCV but not HBV infection in type 2 diabetic patients in Turkey. *Int J Clin Pract.* 2002; 56: 175-177.
4. Chen HF, Li CY, Chen P, See TT, Lee HY: Seroprevalence of hepatitis B and C in type 2 diabetic patients. *J Chin Med Assoc.* 2006; 69: 146-152.
5. Gray H, et al. High prevalence of hepatitis C infection in Afro-Caribbean patients with type 2 diabetes and abnormal liver function tests. *Diabetes Med.* 1995; 12: 244-249.
6. Fukui M, Kitagawa Y, Nakamura N, Yoshikawa T: Hepatitis C virus and atherosclerosis in patients with type 2 diabetes. *JAMA.* 2003; 289: 1245-1246.
7. Hui JM, et al. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression [corrected]. *Gastroenterology.* 2003; 125: 1695-1704.
8. Simo R, et al. High prevalence of hepatitis C virus infection in diabetic patients. *Diabetes Care.* 1996; 19:998-1000.
9. Grimbart S, Valensi P, Levy Marchal C: High prevalence of diabetes mellitus in patients with chronic hepatitis C: a case control study. *Gastroenterol Clin Biol.* 1996; 20: 544-548.
10. National Blood Bank Data for HCV seropositivity in Yangon General Hospital, Yangon, Myanmar. 2006.
11. Shlimovich PB, Zus' BA, Evdokimov AR: Clinical picture and pathogenesis of Diabetes Mellitus in Chronic Hepatitis and Cirrhosis of the liver. *Probl Endokrinol (Mosk).* 1977; 23(4):7-14.
12. Younas BB, Khan GM, Chaudhary MA: Prevalence of diabetes mellitus among patients suffering from chronic liver disease. *Mother and Child.* 2000; 38 (1): 37-40.
13. Mehta SH, et al. Prevalence of type 2 diabetes mellitus among persons with hepatitis C virus infection in the United States. *Ann Intern Med.* 2000; 133(8): 592-9.
14. Caronia S, et al. Further evidence for an association between noninsulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology.* 1999; 30(4):1059-63.
15. Cacoub P, et al. Extra hepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. *Arthritis Rheum.* 1999; 42(10): 2204-12.
16. Mason AL, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology.* 1999; 29:328-33.

Table 1: Biochemical parameters of liver function status in diabetes mellitus patients with or without hepatitis C virus infection

	HCV positive [n(%)]	HCV negative [n (%)]	P value
ALT			<0.001
Normal	5 (26.3)	66 (81.5)	
Increased 1-2 times	10 (52.6)	15 (18.5)	
Increased > 2 times	4 (21.1)	0 (0.0)	
AST			<0.001
Normal	4 (21.1)	69 (85.2)	
Increased	15 (78.9)	12 (14.8)	
Serum bilirubin			0.003
Normal	13 (68.4)	77 (95.1)	
Increased	6 (31.6)	4 (4.9)	
Alkaline Phosphatase			<0.001
Normal	7 (36.8)	76 (93.8)	
Increased	12 (63.2)	5 (6.2)	
rGT			<0.001
Normal	11 (57.9)	81 (100)	
Increased	8 (42.1)	0 (0.0)	
Prothrombin Time			<0.001
Normal	5 (26.3)	77 (95.1)	
Increased	14 (73.7)	4 (4.9)	

Table 2: Imaging profile of liver in diabetes mellitus patients with or without hepatitis C virus infection

	HCV positive [n(%)]	HCV negative [n(%)]	P value
Liver size			<0.001
Normal	6 (31.6)	66 (81.5)	
Enlarged	13 (68.4)	15 (18.5)	
Liver echogenicity			0.253
Normal	12 (63.2)	62 (76.5)	
Increased	7 (36.8)	19 (23.5)	
Space occupying lesion			0.091
Absent	17 (89.5)	80 (98.8)	
Present	2 (10.5)	1 (1.2)	

Table 3: Background characteristics of diabetes

	HCV positive [n(%)]	HCV negative [n(%)]	P value
Type of diabetes			
Type 1	0	0	
Type 2	19 (100)	81 (100)	
Duration of diabetes			0.530
< 5 years	10 (52.6)	49 (60.5)	
> 5 years	9 (47.4)	32 (39.5)	
Family history of diabetes			0.004
Present	5 (26.3)	51 (63)	
Absent	14 (73.7)	30 (37)	
BMI			0.655
20-25	6 (31.6)	30 (37)	
≥ 25	13 (68.4)	51 (63)	
Mode of therapy			0.007
OHA	12 (63.2)	73 (90.1)	
Insulin	7 (36.8)	8 (9.8)	