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ORIGINAL ARTICLE

ASSOCIATION OF CHRONIC HEPATITIS C AND B VIRUS INFECTIONS WITH DIABETES MELLITUS AMONG ADULT ETHIOPIAN PATIENTS AT ADERA MEDICAL CENTER IN ADDIS ABABA

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ABSTRACT

Introduction: *Chronic hepatitis C and hepatitis B virus infections are pandemic affecting more than 170 million and 2 billion people worldwide, respectively. These infections can lead to cirrhosis, hepatocellular carcinoma, and extra hepatic complications like type 2 diabetes mellitus. In this study, we assessed the association of chronic hepatitis C and B virus infections with diabetes mellitus in adult Ethiopians.*

Patients and Methods: *This cross sectional analytical study was conducted at Adera Medical and Gastroenterology Center in Addis Ababa between September 1 and November 30, 2015. One hundred forty one patients with hepatitis C and 359 patients with hepatitis B viral infection were included in the study upon informed consent and following study approval by the institutional review committee. Data regarding diabetes mellitus risk factors, complete blood count, liver chemistry, fasting blood sugar, and sonography were collected. Hepatitis C and B virus screening was done using rapid antibody test and confirmed by enzyme linked immune-sorbent assay followed by polymerase chain reaction, genotype and viral load testing for treatment. The data were analyzed using SPSS version 20 software and strength of association measured using odds ratio and 95% confidence interval.*

Results*: Among the 141 cases with hepatitis C virus infection, the majority (60.4%) were from Addis Ababa, 63% were males, while 61% were below the age of 45 with overall mean (SD) age of 40.7 (95% CI, 39.6-41.9)) years. Genotypes 4 and 1 were predominant, constituting 70% and 20%, respectively. Type 2 diabetes mellitus was diagnosed among 29.8% and 3.6% of the patients with hepatitis C and B viral infections, respectively.*

Conclusion*: Hepatitis C viral infection is statistically significantly associated with the occurrence of type 2 diabetes mellitus, as compared to those with hepatitis B virus infection, indicating the importance of screening for diabetes mellitus with more rigor among patients with hepatitis C virus infection and vice versa.*

Key words*: Hepatitis C Virus, hepatitis B Virus, Diabetes Mellitus, Ethiopia*

INTRODUCTION

Hepatitis C virus (HCV) affects approximately 170 million people while over 2 billion people are infected with hepatitis B (HBV) worldwide. In Ethiopia, epidemiological studies estimate HBsAg and HCV Ab sero-prevalence to be about 8% and 1% respectively. More than 80% of patients with HCV infection progress into a chronic disease, 20–30% of whom progress to cirrhosis after 10–20 years of follow-up, and some develop hepatocellular carcinoma (1). Although HCV targets at the liver, about 38% of patients with HCV were noted to present with extra hepatic manifestation like cryoglobinemia, membrano-proliferative glomerulonephritis, porphyria cutaneatarda, and diabetes mellitus (DM) (1-5).

Hepatitis B Virus (HBV) also leads to a number of hepatic complications ranging from acute to chronic hepatitis, cirrhosis and hepatocellular carcinoma as well as extra hepatic complications. The cause of these extrahepatic manifestations is generally believed to be immune mediated. The most commonly described include skin rash, arthritis, arthralgia, glomerulonephritis, polyarteritis nodosa, and papular acrodermatitis (2).

As many as 80% of the patients with cirrhosis show glucose intolerance and 10%–20% of them have DM (3). Glucose intolerance has been demonstrated in cirrhotic patients because of insulin resistance caused by a post-receptor defect, decreased binding of insulin to target tissue, and inadequate response of the pancreatic beta cells to appropriately secrete insulin to overcome the defect in insulin action (3-5). Obesity, aging, and genetic factors such as family history

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of DM may also contribute to the development of type 2 DM (6-7). Insulin resistance (IR) and diabetes can develop at any stage of HCV infection by interfering with insulin signalling pathway in hepatocytes, igniting inflammatory response with production of cytokines such as TNF alpha and IL-6 and increasing oxidative stress (8-10). Recent studies have shown TNF alpha to be higher in HCV patients with DM than in non-diabetics. It inhibits insulin-stimulated tyrosine phosphorylation of insulin receptor and insulin receptor substrate 1 in adipocytes stimulates lipolysis, and increases serum-free fatty acids, leading to IR in muscle and liver. It increases hepatic glucose production, and down-regulates genes in adipocytes encoding proteins such as insulin receptor substrate 1, glucose transporter-4, peroxisome proliferator-activated receptors, and adiponectin. In addition, TNF-alpha may reduce beta-cell function by direct toxic effects, further contributing to the development of DM (11,12).

To our knowledge, there is no recent report on the association between HCV as well as HBV and DM in Ethiopia. We, therefore, conducted this study to assess the association between DM and HCV and HBV infections among adult Ethiopians patients.

PATIENTS AND METHODS

This cross-sectional analytical study was conducted at the Adera Medical Center in Addis Ababa, Ethiopia, over a period three months, September 1 through November 30, 2015. The study involved 141 patients with HCV and 359 with HBV infections. HCV or HBV seropositive male and female adult patients who were referred by other health facilities or directly visiting the Center were consecutively recruited after informed written consent was obtained from each patient. The research proposal was also approved by the Institutional Research Review Board. Patients who did not give consent and those with liver cancer, on interferon therapy, with end stage renal disease, who had HBV, HCV, and/or HIV co-infection and women who were pregnant were excluded from the study.

Treating physicians, using a structured questionnaire designed for the study, collected Socio demographic and data on risk factor for DM, including address, marital status, age, gender, family history of DM, and liver disease. Data was also collected on comorbidities like HBV, HCV, and/or HIV co infection, and data obtained on alcohol consumption and body mass index (BMI). HCV and HBV screening was done by rapid antibody test and later confirmed by Emzyme-Linked Immuno-Sorbent Assay (ELISA) using the ARCHITECT i2000SR automated analyzer from Abbott Laboratories (USA). Determination of HCV viral load and genotype was done using TaqMan real time reverse transcriptase Polymerase Chain Reaction (PCR) at Bioscientia GmBH in Germany, as these tests were not available in Ethiopia during the study period.

Data collection also included hemoglobin, white blood cell (WBC), platelet count, fasting blood sugar (FBS), and liver chemistry and sonography results of the patients. Two values of FBS $\geq$ 110mg/dl were considered to be diagnostic of DM. Presence of cirrhosis was assessed by abdominal sonography features and AST to platelet ratio index (APRI) score of >2.0 indicating cirrhosis. The data were analyzed using the Statistical package for Social Sciences (SPSS) version 20 computer software. Odds ratio and 95% confidence interval were used to establish the strength and the significance of the association between variables. A logistic regression model was used to explore the association between HCV, HBV and type 2 DM independent of the other explanatory factors.

RESULTS

Among the 141 cases with HCV infections, males comprised a higher proportion 313(63%) with mean age of 40.7 years and 60.4% of them were from Addis Ababa while majority of those with HBV infection were from out of Addis Ababa. Genotypes 4 and 1 HCV infections were documented in 70% and 20% of the patients, respectively. Type 2 DM was diagnosed among 29.8% those infected with HCV in contrast to 3.6% among those infected with HBV. However, positive family history of DM and fatty liver were observed in only few patients with DM, as well as those with HBV and HCV infections.

Disaggregation of the study participants by their diabetes mellitus status indicated that a slightly higher proportion of female patients, 24(12.8%) than male patients, 31(10%) were diagnosed to have diabetes mellitus. Similarly, a higher proportion of older patients (older than 45 years), 46 (23.4%) than younger patients (younger than 45 years), 9(3%) were diagnosed to have diabetes mellitus. The proportion of patients with HCV who were diagnosed to have diabetes mellitus, 42(29.8) was much higher than the proportion of patients with HBV infection who were diagnosed to have diabetes mellitus, 13(3.6%), as shown in Tables 2 and 3.

Table 1: Socio demographic characteristics of study participants, Adera Medical Center, 2015

Variable	Category	Frequency	Percent
Sex	Male	313	62.6
	Female	187	37.4
Age	<45	303	60.6
	>+45	197	39.4
Address (n=418)	AA	285	60.4
	Oromia	83	17.6
	Amhara	37	7.8
	SNNP	31	6.6
	Others	36	7.6
Abdominal US	Normal	183	38.9%
	Fatty liver	80	17.0%
	CLD	181	38.5%
	Ascites	30	6.4%
Types of Infection	HCV	141	28.2%
	HBV	359	71.8%
ALT status (n=270)	<50IU	147	45.7%
	50-100IU	131	40.7%
	100+IU	44	13.7%
AST status (n=269)	<50IU	102	31.8%
	50-100IU	142	44.2%
	100+IU	77	24.0%
Total		**500**	**100.0%**

Table 2: Socio demographic characteristics of study participants by their diabetic status, Adera Medical Center, 2015

		Diabetes Mellitus				
		YES		NO		Total
Variable	**Category**	**N**	**%**	**N**	**%**	**n**
Sex	Male	31	9.9%	282	90.1%	313
	Female	24	12.8%	163	87.2%	187
Age	<45	9	3.0%	294	97.0%	303
	>+45	46	23.4%	151	76.6%	197
Address	Addis Ababa	39	13.7%	246	86.3%	285
	Others	16	7.4%	199	92.6%	215
Abdominal US	Normal	5	2.7%	178	97.3%	183
	Fatty liver	8	10.0%	72	90.0%	80
	CLD	35	19.3%	146	80.7%	181
	Ascites	3	10.0%	27	90.0%	30
Types of Infection	HCV	42	29.8%	99	70.2%	141
	HBV	13	3.6%	346	96.4%	359
ALT status (n=270)	<50IU	17	11.6%	130	88.4%	147
	50-100IU	26	19.8%	105	80.2%	131
	100+IU	9	20.5%	35	79.5%	44
AST status (n=269)	<50IU	8	7.8%	94	92.2%	102
	50-100IU	33	23.2%	109	76.8%	142
	100+IU	11	14.3%	66	85.7%	77
Total		**55**	**11.0%**	**445**	**89.0%**	**500**

Bivariate analysis: In the bivariate analysis, patients' age, address, ultrasonographical findings, types of viral hepatitis infection and lab results of liver function test (AST) were all found to be significantly associated with diabetes mellitus. Patients who were 45 years or older were about ten times more likely than patients who were younger than 45 years to develop diabetes mellitus [COR 9.95 95%CI (4.74, 20.87)]. On the other hand, patients who came from outside Addis Ababa were less likely than patients from Addis Ababa to develop diabetes millets [COR=0.51, 95%CI (0.26, 0.93)]. The bivariate analysis also indicated that there was a significant association between liver sonography findings and patients' diabetic status. Patients with fatty liver and chronic liver disease findings were about 4 and 9 times, respectively, more likely than their counterparts to be positive for diabetes mellitus, [COR=3.96, 95%CI (1.25, 12.5) and COR=8.53, 95%C) (3.26, 23.30]. Patients with hepatitis C viral (HCV) infections are more than 11 times more likely than patients with hepatitis B viral (HBV) infections to develop diabetes mellitus [COR=11.3 95%CI (5.83, 21.9). Similarly, patients whose lab result of liver function test (AST) were between 50 and 100 IU were more than three times more likely than those whose lab test were below 50 IU to be positive for diabetes mellitus, [COR= 3.56, 95%CI (1.57, 8.08)]. Sex of the patients and lab results of ALT (liver function test) however did not show any significant association with diabetes millets in the bivariate analysis.

Multivariate analysis: Variables that showed association with the outcome variable (diabetes malleus) in the bivariate analysis (with p-value of 0.25 or less) were considered for multivariate analysis to eliminate confounders and to identify variables that are independently associated with diabetes millets. Accordingly, the multivariate analysis revealed that age of the patients and type of viral hepatitis infection were remained to be positively associated with diabetes mellitus after controlling for other variables. All the rest of the variables have lost their significant association in the multivariate model. Patients who were older than 45 years were more than 3 times more likely than younger than 45 years old patients to develop diabetes mellitus, [AOR=3.26, 95%CI, (1.36, 7.82)]. The types of viral hepatitis infection that the patients had was considered as one of the predictors for patients' diabetes status. In this multivariate analysis, patients with HCV infection were more than 4 times more likely than patients with HBV infection to develop diabetes mellitus, [AOR=4.35, 95%CI (1.84, 10.3)] as shown in **t**able 3 and Fig 1.

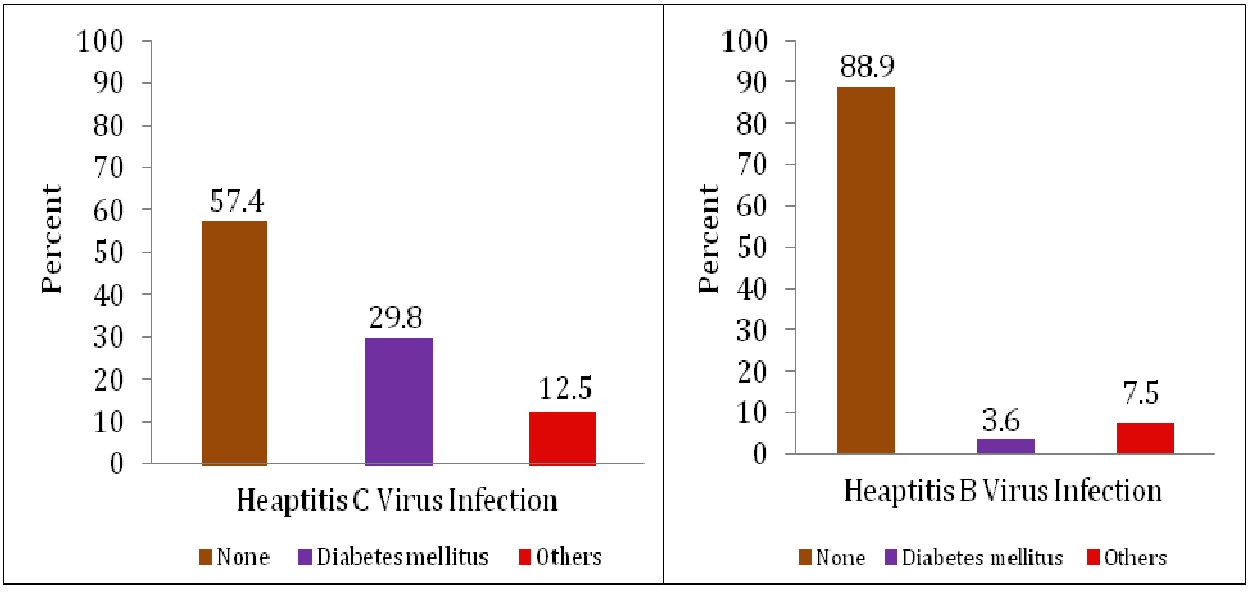

Figure 1. The distribution of co-morbidities among patients with Hepatitis B and C viral infections, Sept.-Nov. 2016, Adera Medical Center, Addis Ababa, Ethiopia

Table 3: Association between viral hepatitis infection and diabetes mellitus among patients attending Adera Medical Center, 2015

Characteristics	Diabetes Mellitus					
	Yes	NO	COR	95%CI	AOR	95%CI
Sex of the patients						
Male	31 (9.9)	2812 (90.1)				
Female	24 (12.8)	163 (87.2)	1.34	(0.76, 2.36)	0.74	(0.36, 1.54)
Age of the patients						
<45 years	9 (3)	294 (97)				
>+45 years	46 (23.4)	151 (76.6)	**9.95**	**4.74, 20.87)**	**3.26**	**(1.36, 7.82)**
Patients' Address						
Addis Ababa	39 (16.7)	246 (86.3)				
Others	16 (7.4)	199 (92.6)	**0.51**	**(0.26, 0.93)**	0.80	(0.39, 1.67)
Abdominal US findings						
Normal	5 (2.7)	178 (97.3)				
Fatty Liver	8 (10)	72 (90)	**3.96**	**(1.25, 12.5)**	1.71	(0.41, 7.16)
CLD	35 (19.3)	146 (80.7)	**8.53**	**(3.26, 22.3)**	1.77	(0.50, 6.26)
Ascites	3 (10)	27 (90)	3.96	(0.89, 17.5)	2.26	(0.37, 13.8)
Type of Hepatitis infection						
HCV	42 (29.8)	99 (70.2)	**11.29**	**(5.83, 21.9)**	**4.35**	**(1.84, 10.3)**
HBV	13 (3.6)	346 (96.4)				
Liver Function Test (ALT)						
<50 IU	17 (11.6)	130 (88.4)				
50-100IU	26 (19.8)	105 (80.2)	1.89	(0.97, 3.67)	1.23	(0.54, 2.81)
>100 IU	9 (20.4)	35 (79.6)	1.97	(0.81, 4.79)	1.46	(0.46, 4.58)
Liver Function Test (AST)						
<50 IU	8 (7.8)	94 (92.2)				
50-100IU	33 (23.2)	109 (76.8)	**3.56**	**(1.57, 8.08)**	1.33	(0.49, 3.62)
>100 IU	11 (14.3)	66 (85.7)	1.96	(0.75, 5.13)	0.68	(0.19, 2.41)

US= ultrasound

DISCUSSION

In our study, patients with HCV infection had type 2 DM at four times higher proportion than patients with HBV infection (29.8% versus 3.6%, respectively). Other potential risk factors like age, family history of DM, and BMI or fatty liver were not significantly different among patients with HCV and HBV infection indicating that HCV is associated with insulin resistance and DM as demonstrated in other international studies (11-12).

Studies from Egypt, Asia, USA, and Europe have shown that 13–33% of patients with chronic HCV infection have associated DM, which is significantly higher than matched controls. Similarly, our study revealed DM to be four times more common among patients with HCV infection than among those with HBV infection after controlling for other risk factors like obesity, aging, and genetic factors such as family history of DM. This is slightly higher association than what has been observed in a population based USA survey conducted in 2000, which revealed that persons older than 40 years of age with HCV infection were 3 times more likely than those without HCV to have type 2 DM.

We have also observed that HCV infection is more common among female patients and tends to increase with increasing age and that hepatitis severity progresses to cirrhosis, which is similar to what has been reported from the West and Asia. This could be due to birth related injuries and blood transfusions, which put women at higher risk than their male counterparts to acquire HCV infection. Unsafe traditional practices like tattooing and ear piercing might have also played additional roles for the higher prevalence. Similar to our previous study, genotypes 4 and 1 were predominant, seen in 70% and 20% of the cases, respectively. However, there is no statistically significant difference noted among various HCV genotypes in developing DM (11-14).

A higher prevalence of DM has also been reported in HCV-infected patients than in chronic hepatitis B, which is in line with our finding. Likewise, DM was noted to be more frequent among patients infected with HCV than with other liver diseases such as primary biliary cirrhosis and primary sclerosing cholangitis (4,10-12). In other studies, the prevalence of DM was also noted to be higher in HCV-positive than in HCV- negative liver transplant recipients as well (15-17). As seen in our study, cirrhotic patients appeared significantly more likely to be diabetic as compared with non-cirrhotic patients in various multivariate analyses (OR=2, 95% CI: 1.15, 3.43). The association of HCV with DM and IR has also been demonstrated in several other previous clinical, epidemiological and laboratory studies (18-26). The studies suggest that HCV promotes IR through viral-associated mechanisms interfering with insulin signaling pathways. The stimulation of various inflammatory processes could also accelerate progression of the pathology leading to worse morbidity and mortality.

This study indicates the need for screening for DM among patients with HCV infection and vice versa to prevent the anticipated chronic complications associated with both conditions, which are associated with substantial morbidity and mortality as well as huge economic burden on patients, their families and the country at large if not treated early before complicated (27).

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