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ORIGINAL RESEARCH

Hepatitis B And Hepatitis C Viral Infections And Associated Factors Among Patients With Diabetes Visiting Gondar Referral Teaching Hospital, Northwest Ethiopia: A Comparative Cross-Sectional Study

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Background: The liver is the major site of Hepatitis B virus and Hepatitis C virus replications. Patients with diabetes tend to be at an increased risk for developing various forms of liver diseases. The infection of the liver can cause or exacerbate diabetes. On the other hand, diabetes can cause or intensify the severity of liver infection. This comparative cross-sectional study was conducted with the aim to determine the prevalence of Hepatitis B and Hepatitis C virus infections and associated factors among patients with diabetes visiting the University of Gondar referral teaching hospital, northwest Ethiopia.

Results: Out of the 610 participants (305 patients with diabetes, 305 people with no diabetes) of the study, 65 (10.7%) were positive for Hepatitis infections, of whom 44 (14.4%) and 21 (6.9%) were positive for at least one of the viruses in patients with diabetes and people with no diabetes, respectively. Out of the diabetic and non-diabetic groups of the study, 26 (8.5%) and 14 (4.6%) (95% CI, 0.96–4.02) were positive for Hepatitis B virus, respectively, while 23 (7.5%) and 7 (2.3%) (95% CI, 1.46–8.68) of the diabetes and non-diabetic groups were positive for Hepatitis C virus, respectively. History of blood transfusion (95% CI, 1.36–12.71) and unprotected sex (95% CI, 1.25–10.15) were significantly associated with Hepatitis B virus infection, while the type of diabetes (95% CI, 1.25–10.89) was associated with anti-Hepatitis C virus positivity.

Conclusion: Positivity for Hepatitis C virus was significantly associated with Type II diabetes. Blood transfusion and unprotected sex were risk factors for Hepatitis B virus infections. Further studies that elaborate temporal associations and find out explanations for the relationship between diabetes and Hepatitis C viral infections are of paramount importance.

Keywords: HBV, HCV, DM, co-infection

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Background

In adult, Hepatitis B Virus (HBV) infection usually resolves and develops protective immunity, but Hepatitis C Virus (HCV) infection tends to progress into a chronic infection in most causalities. The incidence of liver cirrhosis or hepatic cell carcinoma (HCC) is high among individuals with chronic HBV and/or HCV infections.[1,2] Moreover, HCV has been displayed to produce extrahepatic

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manifestations.[3] The World Health Organization (WHO) estimated that about 350 million people are infected with chronic HBV, and 170 million suffer from chronic HCV infection worldwide.[4–6]

Diabetes mellitus is a disease condition that encompasses a group of metabolic disorders regarded as hyperglycemia following irregularities in the secretion or action of insulin or both According to American Diabetes Association (ADA), there are three ways to diagnose diabetes are possible: Symptoms of diabetes plus casual plasma glucose concentration greater than or equal to 200 mg/dL (11.1 mmol/), Fasting Plasma Glucose (FPG) greater than or equal to 126 mg/dL (7.0 mmol/L) and 2 hrs post-load glucose greater than or equal to 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT).[7] It has been perceived to be rigorously linked with advanced age, obesity, and lack of exercise. On the other hand, studies have shown that hepatitis might contribute to the development of diabetes.[8,9] Conversely, a study highlighted that diabetes patients are at high risk for the infection because they are subjected to more frequent medical interventions.[10]

The liver contributes a significant part in glucose metabolism. Hence, efficient liver function is vital to retain glucose homeostasis. The International Diabetes Federation (IDF) estimated that 415 million adults had diabetes and that the digit will rise to 642 million by 2040. Thus, diabetes has grown into a serious public health problem.[11]

The seroprevalence of hepatitis B and hepatitis C has been studied among people with a low sensitive method, rapid test kit, in a non-comparative way and on a small sample which was difficult to reach a conclusion about hepatitis infections among diabetic and non-diabetic groups, especially in our study area. We thus determined the prevalence of HCV and HBV infection among diabetic and non-diabetic people.

Methods

A comparative cross-sectional study was conducted from October 2016 to February 2017 at the University of Gondar referral teaching hospital, northwest Ethiopia. The hospital had a range of specialties, 400 beds, over 400 staff and provides referral services to about five million people in the region. The diabetic clinic at the University of Gondar referral teaching hospital was established in 1985 and has been giving services to 5022 registered DM patients and 3024 of them were type II victims.

Diabetes mellitus patients who were on treatment and visiting the diabetic clinic for check-ups were systematically recruited. Voluntary blood donors at the University of Gondar referral teaching hospital with FBS < 100 mg/dL or RBS <126 mg/dL were considered as a comparative group.

The sample size was determined by using the double population proportion formula, considering 80% power and a 95% confidence interval. Systematically selected 305 diabetic patients and 305 age-sex wise matched volunteer blood donors were conveniently selected and included. The study was carried out according to the declaration of Helsinki for human experimentation and ethically cleared by the Departmental Research and Ethics Review Committee (DRERC) of Addis Ababa University, College of Health Sciences, School of Allied Health Sciences, and Department of Laboratory Sciences. After explaining the aim of the study and the possible need for blood tests, written informed consent was obtained from participants. Two senior nurses collected the socio-demographic and other associated data by using a structured and pretested questionnaire.

A senior laboratory technologist collected 5 mL of venous blood sample using sterile disposable vacutainer tube left for 30 mins to facilitate clotting, and the clotted blood was centrifuged to separate the serum from the blood. The serum was divided into two aliquots. One of the aliquots was used for anti-HCV antibody screening as per the manufacturer's instructions (Anti-HCV cassette, Linear Chemicals SL, Barcelona, Spain). The other aliquots were used for the serologic status of HbSAg. ELISA was used to measure both hepatitis B surface antigen (HBsAg) and anti-HCV. SPSS version 20 software was used to enter, clean and analyze the data collected. Our study used Student's *t*-test for continuous variables and Chi-square for the categorical types. A multivariate logistic regression model was fitted taking two or more of the independent variables into consideration to simultaneously determine the value of the dependent variable for each subject.

Results

Socio-Demographic Characteristics

Diabetic patients were enrolled systematically while they were on follow-ups either for glucose monitoring or treatments, and clients who had medical check-up or diagnosed with disease conditions other than DM were recruited as a comparative group. Thirteen participants who had random blood glucose of greater than 160 mg/dL were excluded from the study. In this study, a total of 610 participants

(305 diabetic, 305 non-diabetic) were enrolled. The mean age was 37.7 and 36.3 years among diabetic patients and non-diabetic groups, respectively. The majority, 56.4% of the diabetic and 59.7% participants, were male. Among individuals who were tested with HBV and HCV serology, no significant differences were observed in terms of age and sex between the groups (p=0.056 and p=0.412, respectively). The mean duration of diabetes was 6.38 ± 5.29 (range 1–22) years, and the mean random blood sugar for the comparative group was 89.43 ± 9.05 mg/dL, "Table 1".

Table 1 Socio-Demographic Characteristics Of Participants With Diabetes And Non-Diabetes Investigated For Burden Of HBV And HCV In University Of Gondar Referral Teaching Hospital (October 2016–February 2017)

Socio-Demographic Characteristics		No. (%)	
		Diabetes	Non-Diabetes
Age (years)	≤35	110(36.1)	128(42.0)
	36–45	123(40.3)	133(43.6)
	46–55	72(23.6)	44(14.4)
Sex	Male	172(56.4)	182(59.7)
	Female	133(43.6)	123(40.3)
Residence	Rural	74(24.3)	38(12.5)
	Urban	231(75.7)	267(87.5)
Occupation	Self-employed	85(27.9)	75(24.6)
	Driver	23(7.5)	20(6.6)
	House Wife	87(28.5)	18(5.9)
	Student	19(6.2)	20(6.6)
	Farmer	48(15.7)	6(2.0)
	Civil servant	43(14.1)	166(54.4)
Religion	Orthodox	281(92.1)	261(85.6)
	Muslim	20(6.6)	44(14.4)
	Others	4(1.3)	0(0.0)
Ethnicity	Amhara	284(93.1)	294(96.4)
	Others*	21(6.9)	11(3.6)
Educational status	Illiterate	99(32.5)	10(3.3)
	Read and write	24(7.9)	18(5.9)
	Primary and High school	147(48)	135(44.2)
	College/university	35(11.5)	142(46.6)
	Total	305(100)	305(100)

Note: *Oromo and Tigray.

Prevalence Of HBV And HCV Infection

Out of the total 610 participants, 65 (10.7%) were found positive for hepatitis infections, of whom 44 (14.43%) and 21 (6.89%) study participants were positive for at least one of the viruses among diabetes and non-diabetic groups, respectively. The prevalence of HBV infection in diabetic and non-diabetic groups was found 26 (8.5%) and 14 (4.6%) (COR=1.94; 95% CI = 0.99–3.79; P-value = 0.053). The burden of sero-positivity against anti-HCV antibody in diabetic and non-diabetic groups was found to be 23/305 (7.5%) and 7/305 (2.3%), respectively, and the difference was statistically significant (COR= 3.47; 95% CI = 1.47–8.23; P-value = 0.005). Co-infection was observed among 5 (1.64%) of the diabetic group, while none was detected among the non-diabetic group, "Table 2".

Associated Factors For HBV And HCV Infections

With respect to clinical practices, hospital admission (P-value < 0.001), surgical procedures (P-value < 0.001) and Venous or body piercing (P-value = 0.02) showed statistically significant differences between diabetic and non-diabetic groups. In the bi-variable analysis, only blood transfusion (COR= 3.05, 95% CI; 1.12:8.29) and unprotected sex (COR= 2.75 95% CI; 1.15:6.56) were significantly associated with HBsAg sero-positivity, "Table 3". The odds of detecting HBsAg among participants with history of blood transfusion, unprotected sex and circumcision were 4.15, 3.56 and 4.58 times greater than with those who had no such history, respectively, "Table 4". The odds of detecting anti-HCV antibody were 3.69 times greater in T2DM than T1DM (AOR=3.69, 95% CI; 1.25–10.89), "Table 5".

Table 2 Burden Of Hepatitis B And Hepatitis C Virus Infection Among Diabetes And Control Groups At University Of Gondar Referral Teaching Hospital (October 2016–February 2017)

Variables		Diabetic Patients	Non-Diabetic Subjects	COR (95% CI)	AOR (95% CI)	p-value
HBsAg	Positive	26(8.5%)	14(4.6%)	1.94(0.99–3.79)	1.96(0.96, 4.02)	0.06
	Negative	279(91.5%)	291(95.4%)			
Anti-HCV	Positive	23(7.5%)	7(2.3%)	3.47(1.47–8.23)	3.56(1.46, 8.68)	<0.001*
	Negative	282(93.8%)	298(97.7%)			

Note: *Statistically significant association (p-value less than 0.05), p-value is for AOR.

Table 3 Bi-Variable Analysis Of Factors For HBsAg Sero-Positivity Among Diabetes Patients At University Of Gondar Referral Teaching Hospital (October 2016–February 2017)

Clinical And Diabetic Characteristics		HBsAg (−) N (%)	HBsAg (+) N (%)	COR (95% CI)	P-value
History of STD/STI	Yes No	13(4.7) 266(95.3)	2(7.7) 24(92.3)	1.70(0.36,8.00) 1.00	0.49
Multiple sexual partner	Yes No	23(8.2) 256(91.8)	5(19.2) 21(80.8)	2.65(0.91,7.68) 1.00	0.07
History of blood transfusion	Yes No	25(9.0) 254(91.0)	6(23.1) 20(76.9)	3.05(1.12,8.29) 1.00	0.03*
Abortion**	Yes No	25(20.5) 97(79.5)	3(27.3) 8(72.7)	1.45(0.36,5.89) 1.00	0.60
Dental extraction at health facility	Yes No	59(21.1) 220(78.9)	7(26.9) 19(73.1)	1.37(0.55,3.42) 1.00	0.49
Circumcision	Yes No	191(68.5) 88(31.5)	22(84.6) 4(15.4)	2.53(0.85,7.57) 1.00	0.09
Hospital admission	Yes No	206(73.8) 73(26.2)	18(69.2) 8(30.8)	0.80(0.33,1.91) 1.00	0.61
Surgical procedure	Yes No	55(19.7) 224(80.3)	7(26.9) 19(73.1)	1.50(0.60,3.74) 1.00	0.38
Venous or body piercing	Yes No	107(38.4) 172(61.6)	10(38.5) 16(61.5)	1.00(0.44,2.30) 1.00	0.99
Delivery by TBA**	Yes No	35(28.7) 87(71.3)	4(36.4) 7(63.6)	1.42(0.39,5.16) 1.00	0.59
Ear piercing	Yes No	83(29.7) 196(70.3)	11(42.3) 15(57.7)	1.73(0.76,3.93) 1.00	0.18
Uvulectomy	Yes No	143(51.3) 136(48.7)	11(42.3) 15(57.7)	0.70(0.31,1.57) 1.00	0.38
Tattooing on body	Yes No	46(16.5) 233(83.5)	7(26.9) 19(73.1)	1.87(0.74,4.70) 1.00	0.19
Tattooing on gum	Yes No	25(9.0) 254(91.0)	4(15.4) 22(84.6)	1.85(0.59,5.79) 1.00	0.29
Shaving	Yes No	119(42.7) 160(57.3)	12(46.2) 14(53.8)	1.15(0.51,2.58) 1.00	0.73
Contact with jaundiced patient	Yes No	36(12.9) 243(87.1)	6(23.1) 20(76.9)	2.02(0.76,5.38) 1.00	0.15
Frequent alcohol consumption	Yes No	100(35.8) 179(64.2)	12(46.2) 14(53.8)	1.534(0.68,3.44) 1.00	0.30
Unprotected sex	Yes No	45(16.1) 234(83.9)	9(34.6) 17(65.4)	2.75(1.15,6.56) 1.00	0.02*
Type of diabetes	Type I Type II	150(53.8) 129(46.2)	15(57.7) 11(42.3)	1.17(0.52,2.64) 1.00	0.70
Any confirmed diseases other than diabetes	Yes No	59(21.1) 220(78.9)	3(11.5) 23(88.5)	0.49(0.14,1.68) 1.00	0.25

(*Continued*)

Table 3 (Continued).

Clinical And Diabetic Characteristics		HBsAg (−) N (%)	HBsAg (+) N (%)	COR (95% CI)	P-value
Duration of disease(year)	<5 6–10 >11	151(54.1) 74(26.5) 54(19.4)	11(42.3) 9(34.6) 6(23.1)	1.52(0.54,4.32) 0.91(0.31,2.72) 1.00	0.42 0.87
Treatment type	Oral Injection Total	94(33.7) 185(66.3) 279(91.5%)	4(15.4) 22(84.6) 26(8.5%)	1.00 2.80(0.94,8.34)	0.66

Notes: *Statistically significant association (p-value less than 0.05), **= concerning female.
Abbreviations: COR, crude odds ratios; CI, Confidence Interval.

Table 4 Multi-Variable Analysis Of Factors For HBsAg Sero-Positivity Among Diabetes Patients At University Of Gondar Referral Teaching Hospital (October 2016–February 2017)

Clinical And Diabetic Characteristics		HBsAg (−) N (%)	HBsAg (+) N (%)	COR (95% CI)	AOR (95% CI)	P-value
History of blood transfusion	Yes No	25(9.0) 254(91.0)	6(23.1) 20(76.9)	3.05(1.12,8.29) 1.00	4.15(1.36,12.71)	0.01*
Circumcision	Yes No	191(68.5) 88(31.5)	22(84.6) 4(15.4)	2.53(0.85,7.57) 1.00	4.58(1.26,16.66)	0.02*
Unprotected sex	Yes No	45(16.1) 234(83.9)	9(34.6) 17(65.4)	2.75(1.15,6.56) 1.00	3.56(1.25,10.15)	0.01*

Note: *Statistically significant association (p-value less than 0.05).
Abbreviations: COR, crude odds ratios; AOR, adjusted odds ratios; CI, Confidence Interval.

Table 5 Multi-Variable Analysis Of Factors For Anti-HCV Sero-Positivity Among Diabetes Patients At University Of Gondar Referral Teaching Hospital (October 2016–February 2017)

Clinical And Diabetic Characteristics		Anti-HCV (−) N (%)	Anti-HCV (+) N (%)	COR (95% CI)	AOR (95% CI)	P-value
Type of diabetes	Type I Type II	160(56.7) 122(43.3)	5(21.7) 18(78.3)	1.00 4.72(1.70,13.07)	3.69(1.25,10.89)	0.02*
Ear piercing	Yes No	91(32.3) 191(67.7)	3(13.0) 20(87.0)	0.32(0.09, 1.09) 1.00	0.53(0.14,2.10)	0.37
Shaving	Yes No	117(41.5) 165(58.5)	14(60.9) 9(39.1)	2.19(0.92,5.24) 1.00	1.66(0.61,4.54)	0.33
Unprotected sex	Yes No	47(16.7) 235(83.3)	7(30.4) 16(69.6)	2.19(0.85,5.61) 1.00	1.03(0.36,2.95)	0.96
Late diabetic complications	Yes No	145(50.7) 141(49.3)	16(69.6) 7(30.4)	2.25(0.90,5.64) 1.00	1.47(0.54,3.96)	0.45

Note: *Statistically significant association (p-value less than 0.05), p-value is for AOR.
Abbreviations: COR, crude odds ratios; AOR, adjusted odds ratios; CI, Confidence Interval.

Discussion

This study included 610 (305 diabetic patients, 305 comparative group) participants grouped according to their blood glucose values. We compared the prevalence of HCV and HBV infection among the participants, and 10.7% of them were found positive for hepatitis infections, whereas 14.43% and 6.89% were sero-positive for at least one of the viruses among diabetic and comparative groups, respectively. Hospital admission, surgical procedures, and venous or body piercing were among significant differences observed among the groups. History of blood transfusion, unprotected sex, and circumcision were the possible factors which were

significantly associated with HBV infections. T2DM was significantly associated with anti-HCV positivity. Therefore, diabetic patients were more likely to get HCV infection. This might be related to either the disease itself or to the fact that patients who were infected with HCV might have developed diabetes owing to extrahepatic effects of the virus.

A study conducted in the USA from 1999 to 2010 using the enzyme-linked immunoassay and chemiluminescent immunoassay for the detection of HBc indicated a prevalence of 8.2% (95% CI = 6.8–9.8) HBc sero-positivity for those with diabetes,[12] which is in line with the result of the present study. But a study in China reported a higher prevalence of (13.5%) HBV infection among diabetic patients,[13] as compared to a prevalence of 8.5% in this study. This might be due to cultural variations, socio-demographic, and epidemiological factors.

The magnitude of HBV infection (8.5%) in our work is higher than that of a study in Ghana,[14] Turkey, a study using a third-generation commercial chemiluminescence assay,[26] and in Ethiopia, a comparative cross-sectional study using rapid diagnostic test in 2014,[15] which indicated a prevalence of 5.5%, 3.8%, and 3.7%, respectively. The prevalence of HBV infection we detected turned out to be higher than that of Woldiya general hospital might be attributed to larger sample size and a higher sensitive diagnostic technique (ELISA) we employed.

The prevalence (7.5%) of HCV infection noted in this study was close to the result of (9.9%) a case–control study at Jimma referral teaching hospital, Ethiopia, screened by a rapid antibody test.[16] Our result was slightly lower than that of Nigeria, 2009 (11%),[17] India, 2016 (11%),[18] Alger, 2012 (12.9%),[19] and Pakistan, 2010 (13.7%),[20] whereas it was much lower than reports from Iraq, 2015 (15%),[21] DHQ teaching hospital, 2014 (27.38%)[22] and Egypt, 2007 (32%).[23] On the other hand, a higher burden (7.5%) of HCV infection we found was higher compared to that of Sudan, 2014 (1.7%),[24] Saudi, 2016 (1.9%),[25] and Turkey, 2015 (3.8%).[26]

In our study, the likelihood of detecting anti-HCV antibody was 3.69 times greater in T2DM than T1DM (AOR= 3.69, 95% CI; 1.25:10.89), which was in line with that of tertiary care hospital, India, which showed all were T2DM.[18] Also, HCV infection was detected in one-third of patients with T2DM in DHQ teaching hospital, Pakistan.[22] Thus, a higher burden of HCV infection in T2DM can explain the fact that HCV infection contributes to the insulin receptor and insulin signaling defects, leading to T2DM.[27,28]

In the present study, blood transfusion, unprotected sex, and circumcision were significant predictors of HBV infection. But in other studies, history of invasive procedures and chronic liver disease, duration of diabetes mellitus, poor diabetic regulation, and insulin treatment usage were associated with HBV infection.[15] Even though this study did not detect any significant epidemiological factors of HCV infection, other studies showed factors associated with HCV infections among DM patients. These included sharing materials, elevated transaminases, exposure to blood or its products, disease duration, tattooing, blood transfusion, and hospitalization more than two times.[25]

Conclusion

The difference in the prevalence of sero-positivity against anti-HCV antibody in diabetic and control groups was statistically significant. The association between Hepatitis C virus infection and type II diabetes in the region was statistically significant. Hence, the absence of a single significant predictor for anti-HCV positivity in diabetes group indicates that HCV might have a role in the pathogenesis of diabetes. History of blood transfusion and unprotected sex were significantly associated with HBV infection.

Abbreviations

Ab, Antibody; Ag, Antigen; ALP, Alkaline Phosphatase; AST, Aspartate Transaminase; CDC, Center for Disease Control; CHB, Chronic Hepatitis B Infection; CLD, Chronic Liver Disease; DM, Diabetic Mellitus; DNA, Deoxy Ribose nucleic acid; EIA, Enzyme Immunoassay; ELISA, Enzyme-Linked Immune Sorbent assay; HAV, Hepatitis A virus; HBc, Hepatitis B core; HBIG, Hepatitis B immune Globulin; HBsAg, Hepatitis B surface Antigen; HBV, Hepatitis B Virus; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C Virus; OPD, Out Patient Department; RNA, Ribose Nucleic Acid; SOPS, Standard Operating Procedures; T1DM, Type 1 Diabetic Mellitus; T2DM, Type 2 Diabetic Mellitus; TMB, 3, 3′, 5, 5′-Tetramethylbenzidine.

Ethics Approval And Consent To Participate

Ethical clearance was obtained from the Department Research and Ethics Review Committee (DRERC) of Addis Ababa University, College of Health Sciences, School of Allied Health Sciences, Department of Laboratory Sciences with a protocol number of DRERC/224/16/MLS and the study was conducted in accordance with the declaration of Helsinki.

Then, permission was obtained from the University of Gondar referral teaching hospital to access data from the study population. All eligible participants were informed that participation was voluntary and personal information obtained was coded to maintain confidentiality.

Availability Of Data And Material

The datasets used and/or analyzed during the study are available from the corresponding author on reasonable request.

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Author Contributions

YM designed and implemented the study, collected data, undertook statistical analysis, performed data interpretation, and drafting the manuscript. TT, SA, TB, AF and KD participated in data analysis and data interpretation and reviewed the manuscript. All authors contributed toward the data analysis, drafting, and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

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