Nigerian Journal of Clinical Practice
June 2008 Vol 11(2):94-99

HEPATITIS C VIRUS INFECTION IN NIGERIANS WITH DIABETES MELLITUS

S. C. Nwokediuko, J. M. Oli
Department of Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria

ABSTRACT

Background/Aims**:** Studies from mainly Caucasian populations have shown epidemiological evidence of an association between diabetes mellitus and Hepatitis C virus (HCV) infection. The aim of this study was to determine whether any such association exists in a black African population with diabetes mellitus.

Method: This was a cross sectional study of consecutive diabetic patients seen at the diabetes clinic of the University of Nigeria Teaching Hospital Enugu, Nigeria between September 1, 2004 and April 30, 2005. Patients who underwent upper gastrointestinal endoscopy during the same period for dyspeptic symptoms were used as controls after matching for age and sex. Structured questionnaire on risk factors for HCV infection was administered to the participants. Blood test for HCV antibodies was carried out on the diabetic patients as well as the control subjects.

Results: Out of 191 diabetic patients, 27(14.1%) were HCV antibody positive compared to the control group in which 5 out of 134 (3.7%) subjects had HCV antibodies ($p = 0.0046$).

Conclusion: Hepatitis C virus infection is more common in Nigerian patients with diabetes mellitus than in control subjects. The nature of the association between diabetes mellitus and HCV infection remains to be elucidated.

Keywords: Hepatitis C virus, Diabetes Mellitus *(Accepted 3 April 2007)*

INTRODUCTION

Diabetes mellitus is a metabolic disease of multiple etiologies characterized by chronic hyperglycemia that is caused by defects in insulin secretion, insulin action or both. It is one of the most important non communicable diseases in Nigeria with a prevalence of 2.2 % [1]. Hepatitis C virus (HCV) infection is a major cause of chronic liver disease. Its prevalence in Nigeria is not known but studies across the country on blood donors indicate a prevalence of 0.4% to 10.4% [2-6]. The virus mainly affects the liver but also several tissues outside the liver have been reported to be involved resulting in a wide spectrum of extrahepatic manifestations [7,8]. Diabetes mellitus has been included in the list of such extrahepatic manifestations of HCV infection. Studies have found a higher prevalence of HCV antibodies in diabetic patients than expected in the general population [9-12]. This study aims at determining whether any such association exists between HCV infection and diabetes mellitus in a typical black African population. diabetic patients and patients with dyspepsia

PATIENTS AND METHODS

This was a cross-sectional study of consecutive (controls) at the University of Nigeria Teaching Hospital, (UNTH) Enugu, Nigeria between September 1, 2004 and April 30, 2005. The study was approved by the Research Ethics Committee of the hospital and informed consent obtained from all the participants before enrolment in the study.

Diagnosis of diabetes mellitus was based on World Health Organization (WHO) criteria [13]. Structured questionnaire was administered to all the participants. The questions included information relating to putative risk factors for HCV infection such as intravenous drug abuse, history of blood or blood product transfusion, haemodialysis, tattooing, birth and scarification marks and household contacts. Venous blood was obtained from all the participants for HCV antibody test using a 3rd generation enzyme linked immunosorbent assay (ELISA) which utilises recombinant HCV antigen HCV (Anti) manufactured by DRG International, Marburg Germany. This

Correspondence: Dr S. C. Nwokediuko
E mail: scnwokediuko@yahoo.com

diagnostic kit has a sensitivity of 95% , specificity of 97.5% and coefficient of variation of 15% .Hepatitis B surface antigen (HBsAg) was also tested for in the diabetic patients and control subjects using Microwell ELISA HBsAg manufactured by Diagnostic Automation Inc. California, U.S.A This kit has a sensitivity of 99.75% , specificity of 99.92% and coefficient of variation of 6.38%. .

Fasting Blood sugar estimation was done on the control subjects to exclude diabetes mellitus according to World Health Organization (WHO) criteria. Statistical analysis was done using SPPS version 12. Proportions were compared using chi square test at a significance level of < 0.05.

RESULTS

A total of 191 diabetic patients (80 males and 111 females) were enrolled in the study. Their ages ranged from 15 years to 83 years (Mean = 55.8711.84 years). There were 134 dyspeptic patients (69 males and 65 females) and their ages ranged from 18 years to 80 years (mean = 54.43 ± 11.16 years). Tables 1 and 2 illustrate the age distribution of the diabetic patients and the control subjects. Six diabetic patients developed the disease before the age of 30 years (3.1%) whereas 185 (96.9%) developed it at 30 years of age or above. Twenty-seven diabetic patients (14.1%) tested positive for HCV antibodies whereas 5 dyspeptic patients (3.7%) had antibodies to HCV (P = 0.0046). The mean age of the diabetic patients who tested positive for HCV antibodies was 56.44 ± 8.57 years whereas the mean age of the HCV antibody-negative diabetic patients was 55.78 ± 12.31 years. The difference was not statistically significant (P = 0.7880). Twenty one out of 27 HCV antibody-positive diabetic patients were females while the remaining 6 were males. The difference was not statistically significant (P = 0.0504). Table 3 shows the HCV antibody status of the diabetic patients. Amongst the 5 HCV antibody positive control subjects (patients with dyspepsia), 3 were females and 2 were males (Table 4). There was no case of dual infection by HCV and HBV. Eight diabetic patients (4.2%) tested positive for HbsAg whereas 5 patients with dyspepsia (3.7%) tested positive for HbsAg (P = 0.8423).As illustrated in table 5, 24 diabetic patients (12.6%) had history of blood transfusion whereas 3 dyspeptic patients had similar history (2.2%). The difference was statistically significant (p = 0.0020). Seventy diabetic patients (36.6%) had history of scarification marks or tattooing whereas 43 control subjects (32.0%) had such history (p = 0.5532). History of receiving injection from medical quacks was Obtained from 104 diabetic patients (54.5%) and 82 dyspeptic patients (61.2%). The difference was not statistically significant (p = 0.5296). History of previous jaundice was obtained in 31 diabetic patients (16.2%) and 9 (6.7%) dyspeptic patients. The difference was statistically significant (p = 0.0220).

A comparison between HCV antibody positive diabetic patients and their HCV antibody negative counterparts (table 6) showed that only 1 HCV antibody positive diabetic patient developed diabetes before the age of 30 years whereas 5 HCV antibody negative diabetic patients developed diabetes before the age of 30 years (p = 0.8512). Twenty six (96.3%) HCV antibody positive diabetic patients developed diabetes when they were already 30 years of age or older whereas 159 HCV antibody negative diabetic patients (97.0%) developed diabetes when they were already 30 years of age or older (p = 0.9818). Family history of diabetes was obtained in 10 (37%) HCV antibody positive and in 66 (40.2) antibody negative diabetic patients (p = 0.8346). Insulin therapy was part of management of 8 HCV antibody positive diabetic patients (29.6%) and 42(25.6%) HCV antibody negative diabetic patients (p = 0.7391).

Table 1:**Age Distribution of Diabetic Patients**

Age (Years)	Number of Patients
10-19	5
20-29	1
30-39	3
40-49	35
50-59	79
60-69	48
70-79	15
80-89	5
Total	**191**

Mean ± SD (years) = 55.87 ± 11.84

Table 2 **:Age Distribution of Dyspeptic Patients Undergoing Upper Gastrointestinal Endoscopy**

Age (Years)	Number of Patients
10-19	3
20-29	1
30-39	2
40-49	29
50-59	62
60-69	28
70-79	8
80-89	1
Total	**134**

Mean ± SD (years) =54.43 ±11.16

Table 3 **: HCV Antibody Status of Diabetic Patients**

Gender	HCV Antibody Positive	HCV Antibody Negative	Total
Male	6 (7.5)	74(92.5)	80(100)
Female	21 (18.9)	90(81.1)	111(100)
Total	27(14.1)	164(85.9)	191(100)

Figures in parentheses = percentages

Table 4 **: HCV Antibody Status of Dyspeptic Patient's**

Gender	HCV Antibody Positive	HCV Antibody Negative	Total
Male	2(2.9)	67(97.1)	69(100)
Female	3(4.6)	62(95.4)	65(100)
Total	**5(3.7)**	**129(96.3)**	**134 (100)**

Figures in parentheses =percentages

DISCUSSION

This study shows that HCV infection is more common in Nigerians with diabetes mellitus (14.1%) than in non diabetic control subjects (3.7%). This finding is similar to that of Simo et al (11) in which 11.5% of diabetic patients and 2.5% of blood donors had antibodies to HCV. A similar study by Mason and his co-workers on a Caucasian population (14) found 4.2% prevalence of HCV infection in diabetic patients and 1.6% in control subjects made up of patients assessed for thyroid disease. The relatively higher prevalence of HCV infection in the diabetic patients in our study (14.1%) may be explained by the different assay methods used for detection of HCV antibodies. In the 2 studies cited above, second generation ELISA was used whereas in our study we used a third generation ELISA which has a better sensitivity and specificity. However, the observation that is common to all the studies including this studys the higher prevalence of HCV infection in diabetic patients than controls. The explanation for this

Table 5 :**Comparisons Between Diabetic Patients And Dyspeptic Patients**

Parameter	Diabetic Patients (n = 191)	Dyspeptic Patients (n = 134)	P- Value
HCV Antibody Positive	27 (14.1%)	5(3.7%)	0.0046*
HBsAg Positive	8(4.2%)	5(3.7%)	0.8423
Scarification/Birth Marks	70(36.6%)	43 (32%)	0.5532
Blood Transfusion	24 (12.6%)	3(2.2%)	0.0020*
Injection from Medical quacks	104 (54.5%)	82 (61.2%)	0.5296
History of Jaundice	31 (16.2%)	9(6.7%)	0.0220*

***Statistically significant**

Table 6 : **Comparisons Between HCV Antibody Positive Diabetic Patients And HCV Antibody Negative Diabeticpatients**

Parameter	HCV Antibody Positive (n = 27)	HCV Antibody Negative (n = 164)	P- Value
<30 years at diagnosis of diabetes	1(3.7%)	5(3.0%)	0.8612
=30 years at diagnosis of diabetes	26(96.3%)	159(97%)	0.9818
Family history of Diabetes	10(37%)	66(40.2%)	0.8346
Insulin therapy	8(29.6%)	42(25.6%)	0.7391

Remains a subject of on-going studies and discussions.

Several studies have shown that the higher prevalence of HCV infection in diabetic patients is not related to most of the main risk factors associated with HCV seropositivity(11,15,16). Those studies specifically showed that diabetic patients with HCV infection and those without HCV infection have the same frequencies of previous blood transfusion. In this study a higher prevalence of previous blood transfusion was demonstrated in diabetic patients than in control subjects (p=0.002). This underscores the epidemiologic fact that in sub-saharan Africa, blood transfusions remain a major cause of the spread of HCV (17-19). Diabetic patients are prone to serious infections occasioned by immunosuppression, which sometimes act in concert with other factors like malnutrition and kidney disease to produce anemia that may be severe to require blood transfusion.Another school of thought contends that HCV infection could cause diabetes through non specific effects on liver cell function. Studies have demonstrated high prevalence of diabetes mellitus in patients with HCV infection [20-22]. As many as 70% of patients with cirrhosis from various causes are glucose-intolerant, and nearly 20% have overt diabetes mellitus, reflecting the role of the liver in carbohydrate metabolism and glucose homeostasis [23,24.] On the other hand there are data suggesting that factors other than liver disease (such as viral factors) may potentially explain some of the diabetes associated with HCV infection. Many HCV-infected persons with diabetes do not have laboratory markers of liver disease such as thrombocytopenia, hypoalbuminemia or hyperbilirubinemia [21,25].HCV infection could also cause diabetes through direct damage to beta cells [26,27] or through virus associated autoimmunity [28] but these mechanisms need further proof. Hepatic steatosis is a characteristic feature of HCV infection [29] and may contribute to HCV-associated diabetes by impairing the ability of insulin to lower hepatic glucose production [30,31] and favouring fibrosis [32,33]. It is possible that several of these mechanisms are necessary in order for HCV infection to lead to diabetes. A prospective study is required to clearly elucidate the exact sequence of events.Using the estimated ages of the diabetic patients at the time of diagnosis, only 6 patients were below 30 years (3.14%) and were presumed to have type 1 diabetes. Even though the current classification of diabetes deemphasizes age as a sole criterion, age at onset of disease still offers a crude guide for classification when there are no facilities for immunological characterization of the disease.

Most of the diabetic patients in this study (94.86%) were presumed to have type 2 disease and that is consistent with the pattern in the general population. This is also in accord with other studies that showed that the association between HCV infection and diabetes is actually stronger in type 2 diabetes than type 1 disease [16,20,25].

The seroprevalence of HCV antibodies in female diabetic patients was 18.9% compared to 7.5% in male diabetic patients. Similarly the seroprevalence of HCV antibodies in female dyspeptic patients was 4.6% compared to 2.9% in male dyspeptic patients. Even though this higher seroprevalence in females did not reach statistical significance, it might be an important finding because it contrasts with studies in the United States which showed that the seroprevalence of HCV antibody is higher in males than females [20]. There is therefore a need for more studies on larger populations to further elucidate this observation.

A comparison was made between the diabetic patients and dyspeptic patients
with respect to the putative risk factors for HCV infection. There was no statistically significant difference between the 2 groups in the use of scarification or birth marks, as well as receiving injection from medical quacks even though these practices were prevalent in both populations. History of jaundice was obtained from more diabetic patients (16.2%) than dyspeptic patients (6.7%). Even though the difference was statistically significant (p=0.022), the exact cause of the jaundice is difficult to speculate because of the multiplicity of causes of jaundice.

One limitation of our study worthy of mention is the fact that HCV infection was diagnosed solely by ELISA .This was not subjected to confirmation by immunoblot assay or direct assays for HCV RNA. Immunoblot tests are now routine in blood banks in the developed world when an anti-HCV positive sample is found by ELISA .

In conclusion, we have established a higher seroprevalence of HCV antibodies in patients with diabetes mellitus compared to non diabetic control subjects. Since cross sectional studies do not establish cause and effect, this study only provides evidence of an association between HCV infection and diabetes mellitus. The clinical implication of HCV infection in diabetic patients is that mild elevations of serum transaminases should not be automatically attributed to fatty liver disease, and, therefore, testing for HCV infection in diabetic patients with an abnormal liver function test should be mandatory. Prospective and cohort studies with prolonged follow-up of patients after a defined exposure to HCV will throw more light on the nature of this association.

ACKNOWLEDGEMENTS
The technical assistance rendered by Mr. Tony Ugwu is highly appreciated. We are also grateful to Dr. Eke Lucy Afuluenu and Dr. Hilda Uzochukwu Ekochin for their assistance in data collection.

REFERENCES

1. **Akinkugbe OO, Akinyanju OO.** Final Report National Survey on Non-communicable disease in Nigeria. Fed. Min. of Health, Lagos 1997; 65-68.

2. **Imoru M, Eke C, Adegoke A.** Prevalence of Hepatitis C Virus (HCV) and Human Immunodefiency Virus (HIV) among blood donors in Kano State, Nigeria. Journal of Medical Laboratory Sciences 2003; 12(1): 59-63.

3. **Erhabor O, Ejele OA, Nwauche CA.** The risk of transfusion-acquired hepatitis C Virus infection among blood donors in Port Harcourt: the question of blood safety in Nigeria. Nigerian Journal of Clinical Practice 2006; 9(1): 18-21.

4. **Koate BBD, Busseri FI, Jeremiah ZA.** Seroprevalence of Hepatitis C Virus among blood donors in Rivers State, Nigeria. Transfusion Medicine 2005; 15(5): 449-451.

5. **Egah DZ, Mandong BM, Iya D, Gomwalk NE, Audu ES, Banwat EB et al.** Hepatitis C Virus antibodies among blood donors in Jos, Nigeria. Annals of African Medicine 2004; 3(1): 35-37.

6. **Mohammed MD.** Serum alanine aminotransferase may not be a good surrogate marker of Hepatitis C virus infection. A study of blood donors in University of Maiduguri Teaching Hospital, (UMTH), Maiduguri. Sahel Medical Journal 2004; 7(3): 88-91.

7 **Gumbert SC, Chopra S.** Hepatitis C: a multifaceted disease: Review of extrahepatic manifestations. Ann Intern Med 1995; 123: 615-620.

8. **Nocente R, Ceccanti M, Bertazzoni G, Cammarota G, Silveri NG, Gasbarrini G.** HCV infection and extrahepatic manifestations. Hepatogastroenterology 2003; 50: 1149 1154.

9 **Ozyilkan E, Erbas T, Simesk H, Telatar F, Kayhan B, Telatar H.** Increased prevalence of hepatitis C virus antibodies in patient with diabetes mellitus. J. Intern Med 1994; 235: 283-284.

10. **Gray A, Wreighitt T, Stratton I. M, Alerander GJ, Turner RC, O'Rahilly S.** High prevalence of hepatitis C infection in Afro-Caribean patients with type 2 diabetes and abnormal liver function tests. Diabet Med 1995; 12: 244-249.

11 **Simo R, Hernandez C, Genesca J, Jardi R, Mesa J.** High prevalence of Hepatitis C virus infection in diabetic patients. Diabetes Care 1996; 19:998-1000.

12. **Ryu JK, Lee SB, Hong SJ, Lee S.** Association of Chronic Hepatitis C Virus infection and diabetes mellitus in Korean patients. Korean J Intern Med 2001; 16: 18-23.

13. Report of expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997;20:1183

14. **Mason AL, Lau YN, Hoang N, Qian K, Alexander GJM, Xu L et al.** Association of Diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999; 29: 328-333.

15. **Rudoni S, Petit JM, Bour JB, Aho LS, Castaneda A, Vaillant G, et al.** HCV infection and diabetes mellitus: Influence of the use of finger stick devices on nosocomial transmission. Diabetes metab 1999; 25: 502-505.

16 **Okan V, Araz M, Aktaran S, Karsligil T, Meran I, Bayraktaroglu Z 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.

17. World Health Organization. Global database on blood safety. Report 2001-2002. http://www.who.int/blood/safety/GDBS_Reopr t-2001-2002.pdf (accessed July 25, 2006).

18. World Health Organization. Global database on blood safety. Summary Report 1998-1999. Http://www.who.int/blood/safety/globaldatab ase /en/sum Rep-English pdf.

19. World Health Organization. Regional Office for Africa. Blood safety strategy for African region. Http://www.who.int/bls/blood-safety/GDBS.pdf. (accessed July 25, 2006.)

20. **Mehta SH, Brancati FL, Sulkowski MS, Strathdee SA, Szklo M, Thomas DL.** Prevalence of type 2 diabetes mellitus among persons with hepatitis C Virus infection in the United States. Ann Intern Med 2000; 133: 592-599.

21 **Grimbert S, Valensi P, Levy-Marchal C, Perret G, Richardet JP, Raffoux C.** High Prevalence of diabetes mellitus with chronic hepatitis C: a case-control study. Gastroenterol Clin Biol 1996; 20: 544-548.

22 **Zein NN, Abdukarim AS, Wiesner RH, Egan KS, Persing DH.** Prevalence of diabetes mellitus in patients with end stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. J. Hepatol 2000; 32: 209-217.

23. **Muting D, Wohlgemuth D, Dorsett R**. Liver cirrhosis and diabetes mellitus. Geriatrics 1969; 24: 91-99.

24 **Petrides AS, Defronzo RA.** Glucose and insulin metabolism in cirrhosis. J Hepatol 1989; 30: 649-654.

25. **Knobler H, Schihmanter R, Zifrouni A, Fenakel G, Schattner. A.** Increased risk of type 2 diabetes in non cirrhotic patients with chronic hepatitis C virus infection. Mayo Clin Proc 2000; 75: 355-359.

26. **Yan FM, Chen AS, Hao F, Zhoa XP, Gu CH, Zhao LB et al.** Hepatitis C Virus may infect extrahepatic tissues in patients with hepatitis C. World J Gastroenterol 2002; 6: 805-811.

27. **Masini M, Campani D, Boggi U, Menicagli M, Funnel N, Pollera M. et al.** Hepatitis C Virus infection and human pancreatic beta cell dysfunction. Diabetes care 2005; 28: 940-941.

28. **Hieronimus S, Fredenrich A, Tran A, Benzaken S, Fenichel P**. Antibodies to GAD in chronic hepatitis C patients. Diabetes care 1997; 20: 1044.

29. **Rozario R, Ramakrishana B.** Histopathological study of chronic hepatitis B and C: a comparison of two scoring systems. J Hepatol 2003; 38: 223-229.

30. **Castera L, Chouteau P, Hezode C, Zafrani ES, Dhumeaux D, Pawlotsky JM.** Hepatitis C Virus-induced hepatocellular steatosis. Am J Gastroenterol 2005; 100: 711-715.

31. **Abid K, Pazienza V, de Gottardi A, Rubbia-Brandt L, Conne B, Pugnale P, et al.** An invitro model of hepatitis C virus genotype 3a-associated triglycerides accumulation. J Hepatol 2005; 42: 744-751.

32 **Camma C, Bruno S, Dimarco V, Di Bona D, Rumi M, Vinci M, et al.** Insulin resistance is associated with steatosis in non diabetic patients with genotype 1 chronic hepatitis C. Hepatology 2006; 43: 64-71.

33. **Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A et al.** Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. Hepatology 1999; 29: 1215-1219.