The relationship of Hepatitis C and B with diabetes of Yemeni patients

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ABSTRACT

Many of earlier reports suggest a connection between hepatitis C virus (HCV) infection and type2 diabetes (T2D). However, the results are conflicting. The aim of our study was to investigate the seroprevalence of both HCV infections and hepatitis B virus (HBV) in type 2 diabetes mellitus (DM) patients in Yemen as well as the risk of hepatitis for development diabetes mellitus. 120 patients were enrolled for this study: 50 patients with T2D, 70 with chronic hepatitis (29 with HCV, 36 with HBV and 5 were infections with HCV and HBV) along with 50 healthy control. Investigated hepatitis C and B patients for blood sugar, determined hepatitis B surface antigen (HBsAg) and anti-HCV in both groups, measured by chromatographic and enzyme-linked immunosorbent assay (ELISA). We found that in T2D-patients 7 out of 50 (14%) detected with hepatitis, 5 (10%) of 50 T2D-patients had evidence of HCV infection compared to 2 (4%) with HBV. The development of type 2 diabetes mellitus among 70 hepatitis C and B patients 8 out of 70 (11.4%), 3 HBV 36 (8.3%), 4 HCV 29 (13.7%), 1 Co-infection HBV and HCV 5 (20%) compared to 1 (2%) without association in 50 control adults. The antibodies levels in T2D-patients with HCV viremia were significantly higher than those in HBV patients. HCV viremia, sex, age, family history of diabetes and tobacco use was found to be difference independent risk factors for diabetes.

Keywords: Hepatitis C, Diabetic mellitus, Hepatitis B, Risk factor, Yemen.

Introduction

Liver is the primary site of hormone and glucose metabolism, and the intercommunication between liver and diabetes has long been recognized. The majority of patients with cirrhosis have glucose intolerance (60%) or overt diabetes mellitus (DM, 20%) [1]. In the Middle East, reliable data upon this subject are scant, however, based on the few available reports, the prevalence of DM is in the range of 4–14% [2,3]. This variation may be partly due to the use of different criteria for diagnosis rendering comparison between countries difficult. The prevalence of type 2 diabetes mellitus in population of Yemen, according to the 1999 WHO was found to be 4.6% [4].

Hepatitis C virus (HCV) seems to increase the risk of incident type 2 diabetes (DM) in predisposed individuals [5]. A linkage between type2 diabetes and chronic hepatitis C virus (HCV) infection, however, the presence of additional factors such as obesity, aging or cirrhosis prevents the establishment of a definite relationship between these 2 conditions [6]. HCV interferes with glucose metabolism independently of age and stage of liver disease, but it is during the cirrhotic stage that multiple factors contributing to insulin resistance may prevail and mask the HCV-related effect [7]. A higher prevalence of HCV infection has been reported in Spain in diabetic patients (11.5%) in comparison with blood donors (2.5%) [8]. On the other hand, 4.2% of patients from a diabetes clinic in North America, were found to be positive for anti-HCV antibodies, compared with 1.6% in the control patients [9]. Yemen near to the Middle East region, where the disease exists with different degrees of prevalence, from low to high.
endemicity, and prevalence varies from 2% to 20%[10,11]. Most studies conducted in Yemen to establish the prevalence of HBV (12—18.5%) have been undertaken in tertiary health care settings [10,12] and have included patients with acute or chronic hepatitis admitted to hospital or blood donors [13,14]. HCV, HBV infections and diabetes mellitus have become major public health problems, approaching epidemic magnitude worldwide. In view of their strong association with each other and there has been no previous study the relationship of hepatitis C or B in type 2 DM patients in Yemen. The objectives of this study were to estimate the association rates of hepatitis C and B in type 2 DM patients in Yemen. The diabetes patientsstrictly diagnostic under treatment by supervision doctors in clinical and hospitals at Taiz and Ibb city—Yemen. Blood samples were taken in random and doctors in clinical and hospitals at Taiz and Ibb city—Yemen. Blood samples were taken in random and fasting states patients, plasma glucose was measured using spectrophotometer, (random blood glucose 120±190mg/dl as diabetes). Venous blood sample were taken from hepatitis patients in random state for plasma glucose study. Venous blood sample were taken from diabetes patients for testing for hepatitis B surface antigen (HBsAg) by enzyme-linked immunosorbent assay (ELISA) (Abbott-Murex, HBsAg, Version 3.0; Murex Biotech Limited, Central Road, Dartford, UK) and testing for anti-HCV antibodies by ELISA (Abbott-Murex, Anti-HCV, Version 4.0, Murex Biotech Limited) according to the manufacturers’ instructions.

All patients were chronic carriers with excluded acute liver disease, liver cirrhosis and fibrosis also cancer patients. The data were expressed as the number and percent. Comparisons between groups were made using the 2x2 contingency table was performed for the categorical variables using the chi square test. A multivariate logistic regression model was used to determine the independent effect of various factors that were potentially associated with the risk of hepatitis. These factors included sociodemographic variables (age, sex, family history of diabetes, tobacco use, and chewing khat) and clinical characteristics (hospital admission, dental operation, blood transfusions and shave at barber). Statistical analyses were performed using SPSS software program version 19. Test probability levels less than0.05 was considered to be statistically significant.

Methods

One-hundred and twenty patients were divided into two comparison groups first group 70 chronic hepatitis C and B patients, second group 50 diabetes mellitus, along with 50 healthy subjects were included as control. The patients were hospitalized and diagnosis confirmed for all cases. At the same time, a questionnaire was used to collect information on the characteristics of hepatitis and diabetes patients which included: age, sex, khat chewing, smoking, family history of diabetes, surgical operation, dental operation and blood transfusions, which were considered as risk factors for diabetic and hepatitis. The diabetes patients strictly diagnostic under treatment by supervision doctors in clinical and hospitals at Taiz and Ibb city—Yemen. Blood samples were taken in random and fasting states patients, plasma glucose was measured using spectrophotometer, (random blood glucose 120±190mg/dl as diabetes). Venous blood sample were taken from hepatitis patients in random state for plasma glucose study. Venous blood sample were taken from diabetes patients for testing for hepatitis B surface antigen (HBsAg) by enzyme-linked immunosorbent assay (ELISA) (Abbott-Murex, HBsAg, Version 3.0; Murex Biotech Limited, Central Road, Dartford, UK) and testing for anti-HCV antibodies by ELISA (Abbott-Murex, Anti-HCV, Version 4.0, Murex Biotech Limited) according to the manufacturers’ instructions.

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Results

Demographic and clinical characteristics of the study subjects

Out of the 120 patients identified, 50 were diabetes patients and 70 were hepatitis C and B virus patients figure (1). Diabetes patients, the baseline demographic and clinical characteristics of the study subjects was shown in tables (1) and (2), while for hepatitis C and B virus patients was shown in tables (3) and (4). Though the development of diabetes mellitus among hepatitis virus slightly slower 11% than prevalence of hepatitis C and B virus among diabetic patients 14%. The major significant in our study was higher prevalence of HCV than HBV among T2D-patients. In the group of control subjects 2, 1 and 1 out of 50 was T2D, HCV and HBV positive, without any association between them. The risk factors (demographic factors) in the tow comparisons groups that suggest enhances developed diseases in both groups that shown in tables (1) and (3), included age, sex, family history of diabetes, tobacco use, chewing khat and clinical characteristics (data not showed) that mounted on questionnaire form. Some differences such as age in T2D—patients with HCV antibodies aged range (60-70 years) with mean (62) while T2D-patients without HCV infection aged range (35-90 years) with mean (54) and in the second comparison group, HCV patients with DM aged between comparisons (42-65) with mean (49.25), while HCV patients with no DM aged between (23-80) with mean (32-42), also family history of diabetes expert less likely differences as in HCV patients with DM positive 50%, while HCV patients without DM 40%, family history of diabetes in T2D-patients with HCV patients 80%, while in T2D-patients without HCV patients 67% and the sex as in T2D-patients with HCV males 60%, while females’ 40% from the subject whom 25 males and 25 females. Tobacco use and
chewing khat was high in T2D-patients with HCV 100% compared with HCV-patients with T2D 50 and 75%.

**Association between hepatitis C and B in type2 diabetic patients (T2DM)**

Overall, the association between hepatitis C and B viruses was diagnosed in 7 out of the 50 subjects of T2DM (14%), while the developing of DM in hepatitis C and B was 8 out of 70 subjects (11%), but compared to healthy control, the HCV infection was higher prevalence [5 (71%) odds ratio(OR) = 5.44;95% confidence interval (CI):0.61-48.3; p = 0.09] compared to HBV infection [2 (29%) OR = 2.04; 95% CI,0.179—23.0; p = 0.55] in T2DM. The development of DM in Co-infection hepatitis C and B virus was 1 out of 5 patients (20%), highest than mono infection B and C infections. Prevalence of DM in hepatitis patients was 8 out of 70 (11.4%), [3 HBV 36 (8.3%) OR = 2.8; 95% CI,0.25—33.0; p = 0.37], 4 HCV [29 (13.7%) OR = 7.3; 95% CI,0.83—73.9; p = 0.03]. 1 Co-infection HBV and HCV [5 (20%) OR = 12.25; 95% CI,0.63—234.8; p = 0.04] table 4. In this study we found the significant differences between prevalence HCV and co-infections in T2DM patients and the strict association between HCV and diabetic mellitus, also we found in our investigation in the hospital and clinical records hyperglycemia more elevated in HCV patients with renal dialysis 10 of the70 subjects 14%, but the strong association was between HCV patients and hyperglycemia 8 in 29 (28%) data not showed.

**Figure 1: Profile of the study patients and their categorization based on T2DM and Hepatitis**
Table 1: Demographic data in 50 T2D-patients with and without HCV and HBV infection

<table>
<thead>
<tr>
<th>Group Risk factors</th>
<th>T2D-patients with HCV antibodies, n (%)</th>
<th>T2D-patients without HCV infection, n (%)</th>
<th>T2D-patients with HBsAg, n (%)</th>
<th>T2D-patients without HBsAg, n (%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median in years)</td>
<td>60-70(62)</td>
<td>35-90(54)</td>
<td>55-60(57.5)</td>
<td>35-90(54.7)</td>
<td>0.21 0.43</td>
</tr>
<tr>
<td>Sex</td>
<td>3 (60 %) M</td>
<td>2 (40 %) F</td>
<td>22(48.9 %)</td>
<td>1 (50 %)</td>
<td>24(50 %)</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>4(80%) Yes</td>
<td>1(20%) No</td>
<td>30(67 %)</td>
<td>2(100%)</td>
<td>30 (63 %)</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>5(100%) Yes</td>
<td>1(0 %) No</td>
<td>13(28.2%)</td>
<td>1(50 %)</td>
<td>17(35.4 %)</td>
</tr>
<tr>
<td>Chewing khat</td>
<td>5(100%) Yes</td>
<td>1(0 %) No</td>
<td>32(71.1 %)</td>
<td>1(50 %)</td>
<td>36(75 %)</td>
</tr>
</tbody>
</table>

Statistical difference between T2D patients with HCV antibodies, HBsAg and patients with no evidence for HCV, HBV infection

Table 2: HCV and HBV infection in T2D-patients

<table>
<thead>
<tr>
<th>Subject groups</th>
<th>HCV Antibodies, n (%)</th>
<th>HBsAg, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2D-patients</td>
<td>5(10%)</td>
<td>2(4%)</td>
</tr>
</tbody>
</table>
| Total (n = 50) | 3(60%) | 1(50%)
| Males (n = 25) | 2(40%) | 1(50%)
| Females (n = 25) | 0(0%) | 0(0%)
| Control subjects | 1(2%) | 1(2%)

Table 3: Demographic data in 70 hepatitis patients with and without diabetes mellitus

<table>
<thead>
<tr>
<th>Group Risk factors</th>
<th>HCV antibodies, with DM, n(%)</th>
<th>HCV infection, without DM, n(%)</th>
<th>HBsAg with DM, n(%)</th>
<th>HBsAg without DM, n(%)</th>
<th>Co-infection with DM, n(%)</th>
<th>Co-infection without DM, n(%)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>42-65(49.25)</td>
<td>23-80(32.42)</td>
<td>55-70(63.33)</td>
<td>17-70(32.6)</td>
<td>50</td>
<td>21-45(31.5)</td>
<td>0.37 0.69 0.77</td>
</tr>
<tr>
<td>Sex</td>
<td>M 3 ( 75 )</td>
<td>12(48 )</td>
<td>2 (67 )</td>
<td>1(33 )</td>
<td>27 (1.8)</td>
<td>1(100)</td>
<td>3(75)</td>
</tr>
<tr>
<td></td>
<td>F 1 ( 25 )</td>
<td>13(52 )</td>
<td>1 (33 )</td>
<td>6(18.1)</td>
<td>0(0)</td>
<td>1(25)</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Table 4: T2D-patients with HCV, HBV and co-infection viruses

<table>
<thead>
<tr>
<th>Subject groups</th>
<th>T2D-patients in HCV antibodies, n (%)</th>
<th>T2D-patients in HBsAg, n (%)</th>
<th>T2D-patients with Co-infection HCV and HBV viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 70)</td>
<td></td>
<td>Total (n = 70)</td>
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<tr>
<td></td>
<td>Males (n = 33)</td>
<td></td>
<td>Males (n = 33)</td>
</tr>
<tr>
<td></td>
<td>Females (n = 37)</td>
<td></td>
<td>Females (n = 37)</td>
</tr>
<tr>
<td>Hepatitis C and B viruses</td>
<td>4(13.7%)</td>
<td>3(8.3%)</td>
<td>1(20%)</td>
</tr>
<tr>
<td></td>
<td>3 (75 %)</td>
<td>2 (67 %)</td>
<td>1(100%)</td>
</tr>
<tr>
<td></td>
<td>1(25 %)</td>
<td>1 (33 %)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Discussion

The prevalence of HCV infection obtained in T2D-patients (10%) compared to HBV infection in T2D-patients (4%), similar to our results studies that have noted the prevalence of HCV infection in T2D-patients (3%) in Kuwait, which has a high incidence of type 2 diabetes [12-13]. Reported that the excess of DM risk with HCV infection in comparison to the excess risk observed in infected patients. The rate of seropositive anti-HCV is 2.8 times higher in type 2 DM patients than non-diabetic control and no significant difference was found between type 2 DM patients and the control group for seropositivity of HBsAg (13.5% versus 12.4%) [15]. Data of previous literature and our study shows a strong association between HCV and type 2 diabetes, may be explain the association of type 2 diabetes with HCV due to pathophysiology of HCV-associated T2D consists of a defect in insulin secretion, excessive hepatic glucose production, increased hepatic tumor necrosis factor alpha, and insulin resistance. Emerging evidence in animals and humans has shown that HCV infection induces hepatic steatosis and increases tumor necrosis factor-a level, both resulting in the development of insulin resistance and subsequent type 2 diabetes [16]. However, results of this study enhancing the role of HCV infection in the development of diabetes, support results from previous studies have shown that patients with chronic HCV genotype 4 infection have an increased risk to develop glucose abnormalities [17,18]. This study prevalence HCV infections patients was higher than HBV in T2DM with 13.7% and 8.8% respectively. This indicate the role of HCV virus for induce DM. Our results are in agreement with those of [19] who reported the link that has been established between HCV infection and the excess risk of type 2 DM observed in comparison with HBV infected patients suggests a potential direct viral role in promoting DM risk.[20] was found the prevalence of type 2 diabetes as 31.5% (114 cases) out of 361 hepatitis C seropositive patients. [6]have shown the ability of insulin to lower the plasma glucose level in the HCV transgenic mice was impaired, as observed in chronic hepatitis C patients.
These results provide a direct experimental evidence for the contribution of HCV in the development of insulin resistance in human HCV infection, which finally leads to the development of type 2 diabetes. HCV infection influences the development of diabetes among 153 HCV-infected subjects (20.9%), developed DM after HCV infection, eight of those (25.0%) followed spontaneous clearance and 24/32 with HCV. Other earlier study [13] reported three individuals with HCV developed post-IFN treatment DM and were included in the HCV control group without DM. The demographic factors questionnaire in our study have marked the smoking and chewing khat as risk factor for T2D while sex and tobacco use in hepatitis patients tables 1 and 3. Our results agreement with [7,21,22]with some risk factors for the development of diabetes in hepatitis patients. HCV was currently associated with family history of diabetes, positively in persons with diabetes and inversely in those with IFG, suggesting that family history of diabetes may serve as a cofactor for progression from HCV-associated IFG to diabetes [21]. Patients with DM were significantly older, a higher percentage of diabetics reported family history DM compared with non-diabetics (54% vs 30%)[7]. The association between HCV infection and DM remained highly significant after adjustment for age, sex, ethnicity, BMI, smoking, alcohol use, corticosteroid use and family history of DM (OR = 3.27; 95% CI, 2.01–5.31) [22]. We found statically analysis the sex and tobacco use as the high risk factors. The distribution of gender, family history of diabetes, age and BMI in T2D-patients with HCV viremia was not statistically different from that in T2D-patients with no evidence of HCV infection [12] in agreement with our results table 1 which shown not significantly in T2D sociodemographic. The mean age of the DM group was higher than that of the HCV-DM group and that there were more females in the T2D group than in the HCV-DM group [13]. Similar with our results which family history of diabetes patients lower than prevalence HCV and HBV among hepatitis patients.[13] with some risk factors for the development of diabetes among hepatitis C and B patients lower than prevalence HCV and HBV among diabetic patients, but the major significant in our study higher prevalence of HCV in T2D-patients than HBV infection, and the predisposed DM to develop in HCV infection patient higher than predisposed HCV in diabetes patients.

**Conclusions**

The development of DM among hepatitis C and B patients lower than prevalence HCV and HBV among diabetic patients, but the major significant in our study higher prevalence of HCV in T2D-patients than HBV infection, and the predisposed DM to develop in HCV infection patient higher than predisposed HCV in diabetes patients.

**Conflict of interest statement**

We declare that we have no conflict of interest.

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