Community-based Study of Hepatitis C Virus Infection and Type 2 Diabetes: An Association Affected by Age and Hepatitis Severity Status

Chong-Shan Wang1,2, Shan-Tair Wang2, Wei-Jen Yao3, Ting-Tsung Chang4,5, and Pesus Chou6,7

1 A-Lein Community Health Center, Kaohsiung County, Taiwan.
2 Institute of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan.
3 Department of Radiology, College of Medicine, National Cheng Kung University, Tainan, Taiwan.
4 Division of Gastroenterology, Department of Internal Medicine, National Cheng Kung University, Tainan, Taiwan.
5 Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan.
6 Community Medicine Research Center, National Yang-Ming University, Taipei, Taiwan.
7 Institute of Public Health, National Yang-Ming University, Taipei, Taiwan.

Received for publication December 12, 2002; accepted for publication June 3, 2003.

Past studies of the relation between hepatitis C virus (HCV) infection and type 2 diabetes conflict. The authors aimed to elucidate the relation by using a large community-based sample with a wide range of liver conditions. Between October 1997 and February 1998, 2,327 consecutive subjects (aged ≥35 years) were enrolled at the public health facility in Taiwan. Blood sugar, hepatitis B surface antigen, and antibody for HCV (anti-HCV) were tested. Abdominal sonography was performed on viral-hepatitis-positive subjects. In univariate analysis, older age, lower educational levels, sedentary work, body mass index of ≥25 kg/m², and anti-HCV positivity were significantly associated with type 2 diabetes (p < 0.05), but smoking, alcohol consumption, gender, and hepatitis B surface antigen status were not. In multivariate logistic regression, anti-HCV positivity was strongly associated with type 2 diabetes in subjects aged 35–49 years (odds ratio (OR) = 3.3, 95% confidence interval (CI): 1.4, 8.0) and 50–64-years (OR = 1.6, 95% CI: 1.1, 2.5). Sonographic evidence of fatty liver (OR = 2.4, 95% CI: 1.2, 4.8) and chronic liver disease (OR = 2.0, 95% CI: 1.0, 4.2) in anti-HCV-positive subjects was moderately associated with type 2 diabetes after age and gender adjustment. Data suggest that HCV infection is moderately associated with type 2 diabetes; the association was strongest for subjects aged 35–49 years and increased with severity of the liver condition.

diabetes mellitus; hepatitis B; hepatitis C; liver

Abbreviations: anti-HCV, antibody for hepatitis C virus; CI, confidence interval; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio.

Hepatitis C virus (HCV) infection is the leading cause of advanced liver disease and a major international public health problem (1). There are about 170 million chronic HCV carriers throughout the world (2). The global prevalence of chronic HCV infection averages 3 percent, ranging from 0.1 percent to 5 percent in different countries (2). In the United States, the prevalence of HCV infection is 1.8 percent, affecting an estimated 3.9 million persons nationwide (3). In hyperendemic communities, the prevalence of antibody for HCV (anti-HCV) positivity is as high as 20–40 percent (2, 4). Patients with HCV infection are frequently found to have extrahepatic manifestations, especially with rheumatologic, dermatologic, and renal impairment (2, 5, 6).

Type 2 diabetes is also a major public health problem worldwide (7). It has become more prevalent as people become more obese and live a more sedentary lifestyle (8, 9). Risk factors strongly associated with type 2 diabetes include family history, body fat distribution, age, sex, smoking, and physical activity (8, 9). It has also been suggested that in addition to these genetic, biologic, and demographic factors,
HCV infection is associated with type 2 diabetes (10–15). This association has been deduced from either a higher prevalence of anti-HCV in patients with type 2 diabetes (10, 12–14) or a higher prevalence of type 2 diabetes in patients with HCV infection (11, 15–17). Nevertheless, some studies do not support HCV infection as a trigger factor for type 2 diabetes (18, 19). Most corroborating evidence has been observed among small samples in which two additional factors are present: 1) advanced liver disease, such as cirrhosis and hepatoma; and 2) a history of HCV infection (10, 13, 16). However, cirrhosis itself has been shown to cause glucose intolerance and insulin resistance (20), so it is not clear whether HCV infection, mild or severe, is actually associated with type 2 diabetes. So far, no community-based study that also considers demographic data, anthropometric characteristics, lifestyle factors, and the severity of chronic liver disease has been known to investigate the relation between type 2 diabetes and HCV infection.

A-Lein, a township in southern Taiwan, exhibits hyperendemic hepatitis B virus (HBV) infection and HCV infection but no human immunodeficiency virus infection. The prevalence of anti-HCV positivity and hepatitis B surface antigen (HBsAg) positivity among the adults in this community is 15.0 percent and 11.8 percent, respectively (4). The present study aimed to elucidate the relation between HCV infection and type 2 diabetes by using the population of this community as a sample because it is large enough and includes a wide spectrum of patients with varying degrees of liver inflammation. Substantiation of the virologic association would have important implications for the prevention and treatment of type 2 diabetes and the progression of HCV infection.

**MATERIALS AND METHODS**

A-Lein Township, in southern Taiwan’s Kaohsiung County, has a population of about 30,000. We have conducted mass hepatitis screenings here for HBV infection and HCV infection since January 1996 because of the high hepatoma mortality rate. Positive viral hepatitis subjects were annually called for abdominal sonography to screen for advanced liver disease, including cirrhosis and hepatoma. In this township, at least 70 percent of the adult residents have been screened for HBsAg and antibody for HCV (anti-HCV) infection markers. From October 1997 to February 1998, we screened everyone aged ≥35 years who came to the A-Lein Community Health Center—the township’s only public health facility—regarding diabetes mellitus and viral hepatitis status. This health promotion campaign was approved by the A-Lein Community Health Promotion Committee and was supported through the mass media and community meetings. All participants provided informed consent. The screening included checks for blood sugar, HBsAg, and anti-HCV. In all, 2,362 participants attended the screening, but 35 with dual infections of HBsAg positivity and anti-HCV positivity were excluded from the study because of small sample sizes and poor classification. Thus, 2,327 participants were recruited for the study. All were negative for antibody to human immunodeficiency virus because there were and, as of this writing, still are no participants positive for antibody to human immunodeficiency virus reported in this township.

Demographic (age, sex, educational level, occupation), daily work activity (sedentary or not sedentary), and health behavior (cigarette smoking and alcohol consumption habits) data were obtained by using a questionnaire administered to all participants by physicians or trained nurses. For the present study, an “alcohol consumption habit” meant that the participant consumed more than one drink (each containing the equivalent of 10 g of pure alcohol) per day in the 6 months before the interview. In addition, a participant without a “smoking habit” had never smoked or had quit smoking for more than 6 months. Anthropometric characteristics, including weight and height, were checked before questionnaires were filled in. Injection drug use was not listed in the study because very few in our study population had a drug use habit (4).

Type 2 diabetes was defined according to the 1997 American Diabetes Association criteria as having a fasting blood sugar level of ≥126 mg/dl, having a nonfasting glucose level of ≥200 mg/dl, or using hypoglycemic drugs prescribed by a physician before or at the time of the study. Persons in whom diabetes had been diagnosed before age 30 years were classified as having type 1 diabetes and were excluded from this study. HBsAg and anti-HCV were identified at the Tainan Blood Center of the Chinese Blood Service Foundation. HBsAg was determined by using the Murex (London, United Kingdom) HBsAg (version I) enzyme immunoassay method. Anti-HCV was tested by using the third-generation Murex anti-HCV enzyme immunoassay, which contains antigen from the HCV core and the nonstructural 3, 4, and 5 regions. In the present study, HBsAg positivity was defined as HBsAg positivity/anti-HCV negativity, anti-HCV positivity was defined as HBsAg negativity/anti-HCV positivity, and seronegative was defined as HBsAg negativity/anti-HCV negativity.

For anthropometric measures, body mass index was computed as weight in kilograms (with the participant wearing underclothes and no shoes) divided by height in meters squared. The obesity cutoff value of body mass index was 25 (<25 vs. ≥25). Abdominal ultrasonography was carried out by a single experienced radiologist (W. J. Yao) specially trained in ultrasonography and unaware of the clinical data. A commercially available real-time ultrasound scanner (Toshiba Tosbee, Tokyo, Japan) equipped with a 3.5-MHz convex transducer was used. The severity of chronic liver disease was graded as normal, fatty liver, chronic hepatitis, or liver cirrhosis according to ultrasonographic morphologic parameters described previously (21, 22).

Odds ratios and associated 95 percent confidence intervals were used in univariate analysis to describe the association between the risk factors and type 2 diabetes. Multiple logistic regression was used to identify independent risk factors for type 2 diabetes. Adjusted odds ratios were used in multivariate logistic regression to describe the association between the different risk factors and type 2 diabetes. The data were analyzed with Stata software (23). Statistical significance was set at p < 0.05.
RESULTS

After comparing the characteristics of seropositive and seronegative participants, we found that anti-HCV-positive subjects were more likely to be older, have a low level of education, have a smoking habit, and have an alcohol consumption habit ($p < 0.05$). However, HBsAg-positive subjects were less likely to be older and to engage in sedentary work. Compared with seronegative subjects, anti-HCV-positive subjects also had more type 2 diabetes (odds ratio (OR) = 1.5, 95 percent confidence interval (CI): 1.1, 2.1). On the contrary, no significant association was found between type 2 diabetes and HBsAg-positive subjects. There were also no significant differences regarding sex and body mass index between seropositive and seronegative subjects (table 1).

Because age is an important risk factor for type 2 diabetes, we analyzed the relation of HCV infection and type 2 diabetes by stratified age (figure 1). The analysis showed that anti-HCV-positive participants in the age groups 35–49 and 50–64 years were more likely than seronegative participants to have type 2 diabetes. The anti-HCV-positive subjects in the age group 35–49 years had at least three times the prevalence of type 2 diabetes compared with anti-HCV-negative subjects (OR = 3.3, 95 percent CI: 1.5, 7.6). In the age group 50–64-years, anti-HCV-positive subjects still had 1.6 times the prevalence of type 2 diabetes compared with...
anti-HCV-negative subjects (OR = 1.6, 95 percent CI: 1.01, 2.5). For those aged ≥65 years, anti-HCV positivity was not significantly associated with type 2 diabetes status (OR = 0.9, 95 percent CI: 0.5, 1.5) (figure 1). In these stratified age groups, sex, sedentary lifestyle, habitual smoking or alcohol consumption, and the means of body mass index were not significantly different between anti-HCV-positive and anti-HCV-negative subjects (data not shown).

Odds ratios for type 2 diabetes from multiple logistic regression, stratified by age, with backward elimination, showed that anti-HCV positivity was the significant risk factor for type 2 diabetes in those subjects aged 35–49 years (OR = 3.3, 95 percent CI: 1.4, 8.0) and 50–64 years (OR = 1.6, 95 percent CI: 1.1, 2.5) but not ≥65 years. For those aged 35–49 years, sedentary work (OR = 2.8, 95 percent CI: 1.4, 5.5) was also a risk factor for type 2 diabetes, but being female was protective (OR = 0.3, 95 percent CI: 0.2, 0.6). For those aged ≥65 years, a body mass index of ≥25, being female, and having a sedentary lifestyle were the significant risk factors for type 2 diabetes. HBsAg positivity was not a significant factor in any stratified age group (table 2).

Of the HBsAg-positive and anti-HCV-negative subjects, we checked 87.3 percent of the former and 86.2 percent of the latter by using liver sonography. Sonographic features were classified as normal, fatty liver, and chronic liver disease (including chronic hepatitis, cirrhosis, and hepatoma). The mean ages of the anti-HCV-positive participants with normal sonographic features, fatty liver, and chronic liver disease (including chronic hepatitis, cirrhosis, and hepatoma) were 58.4 (standard deviation, 11.8), 59.8 (standard deviation, 10.6), and 64.6 (standard deviation, 9.4) years, respectively (data not shown). From multivariate logistic regression analysis after adjustment for age and sex, we found that for both anti-HCV-positive and HBsAg-positive subjects with the sonographic feature of fatty liver, there was a significant association with type 2 diabetes (OR = 2.4, 95 percent CI: 1.2, 4.8 and OR = 3.7, 95 percent CI: 1.2, 11.4, respectively). Anti-HCV-positive participants with sonographic evidence of chronic liver disease had a borderline significantly higher prevalence of type 2 diabetes than those whose sonographic features were normal (OR = 2.0, 95 percent CI: 1.0, 4.2; p = 0.054), but this finding was not true for HBsAg-positive participants (table 3).

**DISCUSSION**

In this study conducted in a community with hyperendemic HBV and HCV infection, we found a moderate association between anti-HCV positivity and type 2 diabetes in the age groups 35–49 and 50–64 years, even after adjustment for other well-established risk factors for type 2 diabetes such as age, sex, educational level, health behaviors, sedentary lifestyle, and body mass index. The strongest association was found for those aged 35–49 years, but this group

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### TABLE 2. Odds ratios for type 2 diabetes from multiple logistic regression, stratified by age, in A-Lein, Taiwan, October 1997–February 1998

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Age 35–49 years (n = 794)</th>
<th>Age 50–64 years (n = 829)</th>
<th>Age ≥65 years (n = 704)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AOR†,‡ 95% CI†</td>
<td>AOR 95% CI</td>
<td>AOR 95% CI</td>
</tr>
<tr>
<td>Sex (female vs. male)</td>
<td>0.3 0.2, 0.6*</td>
<td>1.0 0.7, 1.4</td>
<td>1.5 1.0, 2.3*</td>
</tr>
<tr>
<td>Anti-HCV† (positive vs. negative)</td>
<td>3.3 1.4, 8.0*</td>
<td>1.6 1.1, 2.5*</td>
<td>1.0 0.6, 1.6</td>
</tr>
<tr>
<td>HBsAg† (positive vs. negative)</td>
<td>1.8 0.7, 4.5</td>
<td>1.4 0.8, 2.5</td>
<td>0.8 0.3, 2.2</td>
</tr>
<tr>
<td>Body mass index§ (≥25 vs. &lt;25)</td>
<td>1.7 0.9, 3.3</td>
<td>1.1 0.7, 1.5</td>
<td>1.9 1.3, 2.8*</td>
</tr>
<tr>
<td>Sedentary work (yes vs. no)</td>
<td>2.8 1.4, 5.5*</td>
<td>1.0 0.7, 1.5</td>
<td>1.9 1.3, 2.8*</td>
</tr>
</tbody>
</table>

* p < 0.05.
† AOR, adjusted odds ratio; CI, confidence interval; anti-HCV, antibody for hepatitis C virus; HBsAg, hepatitis B surface antigen.
‡ Adjusted for sex, HCV and hepatitis B virus status, body mass index, and sedentary work.
§ Weight in kilograms divided by height in meters squared.
also had the smallest percentage of higher body mass index, the major risk factor for type 2 diabetes (8, 9). The risk of type 2 diabetes was not affected by HCV infection in those aged ≥65 years, perhaps because those who were both anti-HCV positive and positive for diabetes mellitus were more likely to die of advanced liver disease earlier than those who were anti-HCV positive but negative for diabetes mellitus (24). The change in the strength of the association between HCV infection and type 2 diabetes in different age ranges and/or severity of hepatic fibrosis in our study could explain the conflicting results supporting (13, 15, 16) or not supporting (18, 19) the relation between HCV infection and type 2 diabetes found in previous studies.

In the present study, anti-HCV-positive subjects with sonographic evidence of fatty liver and chronic liver disease had a significantly higher prevalence of type 2 diabetes compared with patients whose sonographic features were normal. Moreover, anti-HCV-positive patients whose sonographic features were normal and subjects who were seronegative had a comparable prevalence of diabetes mellitus. This result implies that when HCV infection is in an early stage of progression or when liver sonography appears normal, the risk of type 2 diabetes is insignificantly different from that for seronegative subjects; however, when the infection progresses into fatty liver or chronic liver disease, the risk of type 2 diabetes increases. Sonographic evidence of fatty liver was also strongly associated with type 2 diabetes in both anti-HCV-positive and HBsAg-positive subjects. This finding might have been due to a larger percentage of body mass index of ≥25 in these groups than in the other groups (data not shown), which might have an additive or synergistic effect. Obesity is strongly associated with type 2 diabetes (8, 9), and both obesity and type 2 diabetes are the main causes of nonalcoholic fatty liver disease (25) and are independent predictors for progression to chronic liver disease (26).

The trend of increasing prevalence of type 2 diabetes with severity of sonographic stages in anti-HCV-positive subjects implies that viral inflammatory activity, time duration, insulin secretion, insulin sensitivity, and the interaction with other well-known diabetes risk factors appear to play an important role in the development of type 2 diabetes. Although anti-HCV-positivity in subjects reflects true exposure, about 15–26 percent of anti-HCV-positive subjects are HCV-RNA negative and indicate past infection (2, 27). Subjects whose sonographic features are normal might include more HCV-RNA-negative cases and might have more normal alanine transferase levels and lower histologic activity index scores (27, 28). However, duration of HCV infection might be shorter in the normal sonographic group than in the group with sonographic evidence of chronic liver disease because the mean age of the former group was at least 5 years younger than that of the latter group in this study (data not shown). On the basis of these findings, chronic HCV infection might be associated with diabetes mellitus; therefore, slowing the progression of HCV infection to fatty liver or advanced liver disease by avoiding precipitating factors such as smoking or obesity (25, 29) or undergoing antiviral therapy (2) might also be beneficial in preventing the development of diabetes mellitus.

The present study shows different interactive effects between age and other risk factors for type 2 diabetes. Men had a significantly higher prevalence of type 2 diabetes before age 50 years, but there was no sex difference after age 50 years. This finding might be related to men having had a more abnormal liver status according to sonography than females in the current study (table 3), especially in the age group 35–49 years. A possible explanation is that, compared with women, men had a much higher prevalence of smoking (57.7 percent vs. 1.2 percent) in this study. Habitual smoking is a well-documented risk factor for exacerbation of liver conditions, such as increased alanine transferase levels, rapid changes in the histologic progression of chronic liver lesions, and increased fibrosis and carcinogenesis (29, 30), that would increase the likelihood of type 2 diabetes. Otherwise, women might be more likely to be associated with HCV clearance and lower rates of HCV-RNA positivity (31). However, the likelihood of type 2 diabetes increases sharply after menopause, about age 50 years, because of increased glucose intolerance caused by obesity and hormonal factors (32), which might explain the reversal of the effect of sex in multivariate logistic regression analysis.

The odds are at least 50 percent greater (18.2 percent vs. 12.1 percent) that anti-HCV-positive rather than seronegative participants will have type 2 diabetes. Such a high prevalence of diabetes in anti-HCV-positive subjects suggests

**TABLE 3.** Adjusted odds ratios for type 2 diabetes for seropositive study participants whose sonographic features were abnormal, A-Lein, Taiwan, October 1997–February 1998

<table>
<thead>
<tr>
<th>Sonogram result</th>
<th>Anti-HCV* positive (n = 312)</th>
<th>HBsAg* positive (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DM positive/ DM negative</td>
<td>AOR*,† 95% CI</td>
</tr>
<tr>
<td>Normal</td>
<td>20/144 1.0</td>
<td></td>
</tr>
<tr>
<td>Fatty liver</td>
<td>20/56 2.4</td>
<td>1.2, 4.8</td>
</tr>
<tr>
<td>Chronic liver disease‡</td>
<td>18/54 2.0</td>
<td>1.0, 4.2</td>
</tr>
</tbody>
</table>

* Anti-HCV, antibody for hepatitis C virus; HBsAg, hepatitis B surface antigen; DM, type 2 diabetes mellitus; AOR, adjusted odds ratio; CI, confidence interval.
† Adjusted for age and sex.
‡ Includes chronic hepatitis, cirrhosis, and hepatoma.
the importance of concern for its increasing complications. Comorbidity will also promote the development of glomerulonephritis and cryoglobulinemia and consequently exacerbate kidney function (6, 14). Type 2 diabetes itself is the major cause of nonalcoholic fatty liver disease (25) and in turn causes liver fibrosis (26); therefore, comorbidity might exacerbate a chronic hepatitis C condition and cause a progression to advanced liver disease such as cirrhosis or hepatocellular carcinoma (24). Hence, it is important to eliminate other risk factors for the development of type 2 diabetes in anti-HCV-positive subjects. This consensus is particularly important because obesity and a sedentary lifestyle have been increasing rapidly worldwide in recent decades (7), and HCV infection is the major cause of chronic liver disease in many countries (1).

In this study, HBsAg positivity was not significantly associated with type 2 diabetes, although there was a trend. This result is consistent with those from studies of patients with chronic liver disease and cirrhosis (16, 17). However, the small number of HBsAg-positive participants with chronic liver disease in our sample might have limited our ability to detect the difference. The other possibility might be related to greater necroinflammation, for example, elevated aminotransferase levels, in anti-HCV-positive than in HBsAg-positive participants (40–50 percent vs. 10–15 percent) (26), which means that more HBsAg-positive than anti-HCV-positive participants are healthy carriers. Whether the viral action on B-cell secretion or insulin resistance is different between HBV and HCV infection awaits further study.

Although the prevalence of anti-HCV positivity was similar to that in our previous community-wide screening (4), this study had several limitations. First, we could not confirm the etiologic relation of HCV infection and type 2 diabetes because the source of HCV infection might have been blood contamination caused by increasing medical interventions related to type 2 diabetes (4). However, this possibility seems remote because reuse of needles has been prohibited for the past decade. In addition, because the younger patients were more likely to have developed type 2 diabetes more recently than the older patients, they were less likely to have been subjected to medical intervention. Rather, the younger subjects in this study were more likely to have contracted HCV infection earlier than they developed type 2 diabetes. Furthermore, selection bias might have occurred; those with advanced liver disease or diabetes mellitus might have been treated and followed up at other hospitals or medical centers and so might not have come to our health center for screening.

Second, HCV-RNA was not tested to elucidate the relation between actual viral status or past infection and type 2 diabetes because 15–26 percent of anti-HCV-positive subjects were HCV-RNA negative and indicated past infection (2, 27). However, the strength of the association between HCV infection and type 2 diabetes might have increased after removing these HCV-RNA-negative subjects because they were more likely to have a normal liver biopsy (27). Third, although liver biopsy is indicated to establish the stage of liver disease (33), it is infeasible to perform in a community-wide study because of complications and cost. Sonography, however, can noninvasively predict liver histology with high sensitivity (89–100 percent) and specificity (89–93 percent) (34), and it is both feasible in the community and appropriate for screening and follow-up of patients with chronic liver disease or hepatic fibrosis (21, 22). In addition, misclassification might have occurred regarding sonographic hepatic features because no liver biopsy was conducted to confirm the true condition.

Although neither smoking habits nor alcohol consumption habits were independent risks in multivariate logistic regression analysis for type 2 diabetes or liver status in this study, categorizing these two habits dichotomously might have resulted in a limitation. On the other hand, the risks associated with these two habits might operate on a continuum. Moreover, very few study participants indicated alcohol consumption levels problematic for the liver—three drinks per day for women and five drinks per day for men. In addition, the interacting effect of alcohol consumption on the liver status of HCV infection and the development of type 2 diabetes is inconclusive (33, 35).

HCV but not HBV infection was moderately associated with type 2 diabetes after we adjusted for other risk factors, especially for those subjects aged <65 years. The strength of the association increased with decreased stratified age or increased severity of sonographic evidence of chronic liver disease. A high prevalence of type 2 diabetes in anti-HCV-positive subjects indicates that early intervention for anti-HCV-positive subjects is needed to prevent development of type 2 diabetes and to prevent exacerbation of the complications of comorbidity. Further study is needed to elucidate the etiologic relation.

ACKNOWLEDGMENTS

The authors are indebted to the A-Lein Community Health Promotion Committee and to the C. T. Hsu Cancer Research Foundation for their generous financial support.

The authors thank the staff and volunteers of the A-Lein Community Health Center for their assistance with data collection as well as the Tainan Blood Center of the Chinese Blood Service Foundation for assistance with laboratory analyses.

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