Hepatitis C Infection and Type 2 Diabetes in American-Indian Women

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OBJECTIVE — The aim of this study was to describe the association between hepatitis C virus (HCV) infection and type 2 diabetes among a group of American-Indian women who were screened for both conditions.

RESEARCH DESIGN AND METHODS — The study population was a convenience sample of women who were receiving prenatal care. All women were systematically screened for both HCV and diabetes.

RESULTS — A total of 426 women were included in the sample. HCV infection was detected in 13 (3.1% [95% CI 1.7–5.0]) and type 2 diabetes in 22 (5.2%, [3.3–7.6]) women. Women diagnosed with type 2 diabetes were more obese and had higher serum alanine aminotransferase activity compared with women without diabetes. Four of 13 (30.8% [10.6–58.7]) HCV-infected women and 18 of 413 (4.4% [2.7–6.7]) women without evidence of HCV infection had type 2 diabetes. (odds ratio 9.8 [95% CI 2.4–34.0], Fisher's exact test $P = 0.003$). In a logistic regression model, increasing age (10-year increments), obesity (by standard deviations from the mean BMI), and positive HCV status were each independently related to the diagnosis of diabetes.

CONCLUSIONS — Among American-Indian women, type 2 diabetes is more common in those with than in those without HCV infection. This association and its potential mechanisms may have clinical implications. Investigation into the mechanisms linking HCV infection to the expression of type 2 diabetes may also help to define processes that promote the development of type 2 diabetes in susceptible individuals.

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People with hepatitis C virus (HCV) infection appear to be at increased risk of developing type 2 diabetes (1–14). The impact of HCV infection on the occurrence of type 2 diabetes in American Indians, an ethnic group with high prevalence of type 2 diabetes (15), is unknown. The aim of this study was to describe the relationship of HCV infection to the presence of type 2 diabetes among a group of American-Indian women who were systematically screened for both conditions.

RESEARCH DESIGN AND METHODS

— The Phoenix Indian Medical Center is an inpatient and outpatient Indian Health Service facility located in Phoenix, Arizona. Many different tribal affiliations from around the country are represented among the patient population.

The study population was a convenience sample of women who were receiving prenatal care at the medical center. Prenatal services included the routine screening for hepatitis B virus infection (16). After 1999, the laboratory panel used for screening for hepatitis B virus also included a second-generation hepatitis C antibody. All patients also received a 50-g oral glucose tolerance test during the second trimester of pregnancy, and abnormal screening tests were followed up with a 100-g glucose tolerance test (17). When clinically indicated by the presence of risk factors for diabetes, screening and diagnostic tests for diabetes were performed earlier in pregnancy. Because these women received systematic screening for both hepatitis C and diabetes, this population presented the opportunity to study the relationship between the two conditions.

Women were identified by a three-step review of the computerized hospital information system. First, 2,463 patients who had a second-generation anti-HCV antibody test between 1 October 1999 and 30 September 2000 were identified. Second, we narrowed the sample to 541 patients who had a positive urine pregnancy test within 6 months before the HCV test. Finally, the analysis was further limited to a sample of 426 of these women who had a prepregnancy weight and height recorded to calculate a BMI.

The diabetes status for each patient was further confirmed by electronic search for visits for diabetes preceding, during, and after pregnancy and by matching all 426 patients to an actively maintained Diabetes Registry maintained at the Phoenix Indian Medical Center (18). To confirm the electronic record review and the accuracy of classification, the paper medical record for each patient in the sample identified as having diabetes was reviewed in depth. The 1997 American Diabetes Association criteria for the diagnosis and classification of diabetes were applied to each case to differentiate gestational diabetes from other forms of diabetes and thereby assure a correct diagnosis of type 2 diabetes (19). None of the case subjects of type 2 diabetes had their first abnormal glucose detected during pregnancy. However, had that occurred, the case definition would have required persistence of the glucose abnormality beyond pregnancy. Thus, in this

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Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; NHANES III, Third National Health and Nutrition Examination Survey; TNF-α, tumor necrosis factor-α.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1— *Sample characteristics*

Age (years)	24.9 ± 5.6 (15–44)
Diabetes	5.2 (3.3–7.6)
HCV infection	3.1 (1.7–5.0)

Data are means ± SD (range) or percent (95% CI); $n = 426$.

convenience study sample of women who were receiving prenatal care, the primary use of the glucose tolerance testing was to assure the absence of diabetes in those with normal results. The age at diagnosis of diabetes was determined from historical information in the medical record.

Laboratory measurements

Presence of HCV infection was assessed by testing for serum HCV-specific antibodies (anti-HCV) using a commercial enzyme-linked immunosorbent assay with confirmation by an immunoblot assay on anti-HCV$^+$ samples to confirm HCV specificity.

Additional laboratory data

In addition, the hospital information system laboratory database was queried to identify the most recent alanine aminotransferase (ALT) value if available and if performed between 1 October 1999 and 30 September 2001.

Statistical analysis

Statistical analysis (including prevalence rates, confidence intervals, and odds ratios) were calculated using Epi-Info statistical software (Stone Mountain, GA). The statistical significance of the relationship between HCV and type 2 diabetes was determined by applying Fisher's exact test on the results of a two-by-two table. A multiple logistic regression model was computed using SAS (Cary, NC). In the model, BMI in 10-unit increments, 10 years of age, and ALT were used. Approval for the study was obtained from the Phoenix Area Institutional Review Board.

RESULTS — The demographic and clinical characteristics of the 426 patients included in the sample are shown in Table 1. HCV infection was detected in 13 (3.1% [95% CI 1.7 −5.0]) of the 426 women in the sample. None of the women in the sample had detectable hepatitis B surface antigen. The mean age of anti-HCV$^+$ and anti-HCV$^-$ women in this sample was not statistically different (27.0 ± 6.7 vs. 24.8 ± 5.6 years, $P = 0.37$). There was a trend (χ^2, $P = 0.13$) toward an increased prevalence of anti-HCV with age when comparing women by the following age categories: 15–24 years (2.2% [0.8–4.8]), 25–34 years (3.0% [1.1–6.7]), and 35–44 years (8.3% [2.1–21.0]). Within the study time frame, 11 of 13 anti-HCV$^+$ (84.6%) and 114 of 413 (27.6%) anti-HCV$^-$ women had a determination of serum ALT activity. The mean ALT values of anti-HCV$^+$ and anti-HCV$^-$ women in this sample were not statistically different (37.2 ± 15.3 vs. 41.9 ± 40.9 mg/dl, $P = 0.82$). Among those tested, 1 (9.1%) of 11 anti-HCV$^+$ and 13 (11.4%) of 114 anti-HCV$^-$ women had an ALT greater than the upper limit of normal value of 65 mg/dl for the clinical laboratory.

Type 2 diabetes was confirmed in 22 (5.2% [95% CI 3.3–7.6]) of the 426 women in the sample. Nine additional women had glucose abnormalities consistent with gestational diabetes and were not included in the analysis. Women diagnosed with type 2 diabetes were older than women without a diagnosis of diabetes (29.5 ± 7.1 vs. 24.7 ± 5.4 years, $P = 0.0001$). There was an increased prevalence of diabetes with age (χ^2 for trend, $P = 0.001$) when comparing women by age category: 15–24 years (2.2% [0.8–4.8]), 25–34 years (6.7% [3.6–11.4]), and 35–44 years (16.7% [7.0–31.5]). Women with diabetes were more obese, as measured by BMI (35.4 ± 3.0 vs. 28.5 ± 6.6 kg/m^2, $P = 0.000002$), and had higher serum ALT activity (49.2 ± 24.4 vs. 44.4 ± 41.1 mg/dl, Kruskall-Wallis $P = 0.01$) compared with women without diabetes, but the difference in ALT did not persist after adjustment for BMI.

The association of HCV infection and type 2 diabetes is demonstrated in Fig. 1. Diabetes was present in 4 of 13 (30.8% [95% CI 10.6–58.7]) HCV-infected women and in 18 of 413 (4.4% [2.7–6.7]) women without evidence of HCV infection (odds ratio 9.8 [95% CI 2.4–34.0], Fisher's exact test $P = 0.003$). In a logistic regression model, increasing age (10-year increments), obesity (by standard deviations from the mean BMI), and positive HCV status were each independently related to the diagnosis of diabetes. The addition of serum ALT activity did not affect the model (Table 2).

Table 2—*Logistic regression model*

	Odds ratio estimates	
Effect	Point estimate	95% CI
Age	2.6	1.3–5.4
BMI	2.3	1.5–3.5
HCV	6.7	1.6–27.6

Age is expressed in 10-year increments. BMI: SD increases above the mean. HCV: positive versus negative.

The relative prevalence of type 2 diabetes among women with and without hepatitis C infection, and therefore potentially attributable to hepatitis C infection, is 0.264. Assuming these pregnant women are representative of other members of the population (i.e., nonpregnant women, men, and all other age-groups), a prevalence of HCV of 0.03 results in a population risk of diabetes attributable to HCV infection of 0.264 × 0.03 or 0.008.

CONCLUSIONS — Among American-Indian women, type 2 diabetes occurs more often in women who test positive for HCV infection than in those who test negative. The association between type 2 diabetes and HCV infection

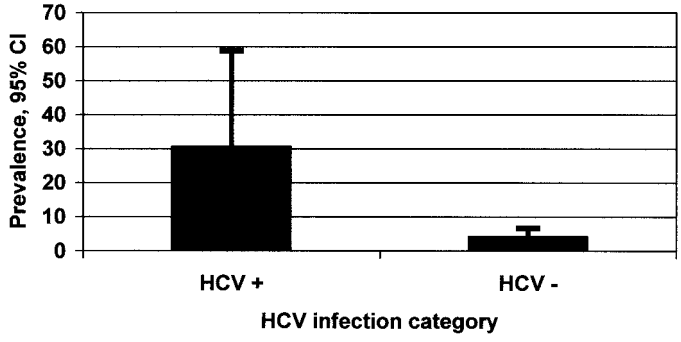

Figure 1—*Prevalence of type 2 diabetes by HCV infection category.*

persisted in logistic regression analyses that included age and BMI. This finding supports the association of HCV infection with type 2 diabetes.

Whereas this was a retrospective study of a convenience sample of women who were undergoing routine prenatal care, the systematic screening process for both HCV and diabetes help to limit potential selection bias. Also, because sample was created from women receiving routine prenatal care as opposed to specialty evaluation for disease, the findings will likely be generalizable to the greater patient population.

HCV is the most common chronic blood-borne infection in the U.S. (20,21). The prevalence of HCV in an American-Indian population has not previously been reported. However, the 3.1% prevalence of HCV infection in this sample of women was within the range reported for the general U.S. population. Specifically, the overall U.S. prevalence among participants in the Third National Health and Nutrition Examination Survey (NHANES III) from 1988–1994 was 1.8% (95% CI 1.5–2.3) but ranged from 1.5 (1.1–2.0) in non-Hispanic whites to 2.1 (1.7–2.6) in Mexican Americans, to 3.2 (2.6–4.0) in non-Hispanic blacks, and 2.9 (2.4–5.8) in other ethnic groups (22). The prevalence of HCV infection in the current study is also within the ranges reported among women being tested as a component of prenatal care from study in various countries. Among a multiethnic population of pregnant women attending an inner London obstetric department, the overall prevalence of anti-HCV reactivity was 0.8% (23). Similarly, among pregnant women in Germany, 0.8% of women were found to be anti-HCV$^+$ (24). The prevalence of HCV infection was 1.5% among women screened during prenatal care in Brazil (25). Among pregnant women attending an inner city clinic in Philadelphia, the HCV prevalence was 4.3% (26). The highest reported prevalence of anti-HCV in a prenatal care population was in Egypt where 19% of women tested positive (27). Thus, the prevalence of HCV among pregnant American-Indian women appears to be within the wide range of rates reported in the literature.

The prevalence of type 2 diabetes in this population was also similar to other reports of American-Indian women of childbearing age (28). In the present study, consistent with many studies, both age and obesity were strongly associated with diabetes (19).

As noted, the recognition of an association between HCV infection and type 2 diabetes has been previously reported. However, this is the first report to demonstrate relationship in an American-Indian population and the first to demonstrate this association in people <40 years of age. Interestingly, the magnitude of the association between HCV infection and diabetes in the current study is similar to the magnitude of the association in high-risk subgroups from the NHANES population (8). The women in the current study are all at increased risk for diabetes because of their ethnicity, which may explain both the high odds ratio and the occurrence in young age-groups.

Several mechanisms may explain the link between HCV infection and type 2 diabetes. Hepatic steatosis and cirrhosis, both features of HCV infection, have been associated with abnormal glucose regulation (29). Steatosis in particular has been related to intracellular fat accumulation and insulin resistance, and along these lines, in Pima Indians, ALT, a marker of steatosis, is predictive of the development of type 2 diabetes (30). In the present study, these young, relatively healthy women would be unlikely to have developed cirrhosis, and the ALT values were not different between those with or without diabetes. Recent animal model evidence suggests a more direct effect of HCV infection on insulin resistance in the liver. Shintani et al. (31) used transgenic mice that specifically express the HCV core protein at high levels in hepatocytes. In these transgenic mice, elevated circulating insulin levels and islet cell hyperplasia were present before the onset of steatosis. Because hepatic tumor necrosis factor-α (TNF-α) is known to be elevated in this animal model (31) and in human HCV infection (32) and to have an effect on insulin signaling (33), the authors evaluated the role of hepatic TNF-α in affecting insulin signaling in this animal model of HCV infection. Indeed, insulin-induced tyrosine phosphorylation of IRS-1 was inhibited in the transgenic mice, and the effect was prevented by administration of anti-TNF-α antibody. Interestingly, euglycemic insulin clamp and muscle glucose uptake studies on these mice demonstrated defective insulin inhibition of hepatic glucose production but normal glucose uptake in muscle. Together, these findings suggest that expression of the HCV core protein induces hepatic insulin resistance via alterations in signaling in the insulin receptor–IRS-1 pathway and that this, along with other factors such as diet and obesity, can result in expression of the diabetic phenotype. Other pathways may also exist (29). In our retrospective study, neither measurement of TNF-α nor markers of the level of activity of HCV infection were available. Future studies should be designed to assess these pathways in humans with HCV infection and diabetes.

The transgenic mouse model and the present study may also provide clues to the prevention and clinical management of diabetes in the setting of HCV infection. In the transgenic mouse model, diabetes only developed when the mice were challenged with a high-fat diet (31). In the present analysis, BMI was associated with diabetes independently of HCV infection. Thus, weight control should continue to be a preventive and therapeutic goal. Also, because defective insulin signaling in HCV infection may be limited to the liver, pharmacologic therapy might logically be tailored to the function of this organ. The biguanide metformin acts primarily by decreasing endogenous glucose production in the liver (34). However, metformin is known to affect insulin signaling via induction of IRS-2, and whether metformin will have any preferential advantage over other commonly used medications for glycemic control in this setting is speculative.

In summary, among American-Indian women, type 2 diabetes is more common in those with than without HCV infection. This association is independent of age and BMI. Because of the low population attributable risk, prevention and treatment of hepatitis C infection is not likely to have a major public health role as a diabetes prevention effort. On the other hand, among those infected, attention to efforts known to delay or prevent the development of diabetes (35) as well as screening for and treatment of diabetes if identified seem particularly warranted. Finally, continued investigation into the mechanisms linking HCV infection to the expression of type 2 diabetes may help to define processes that promote the development of type 2 diabetes in susceptible individuals. Such findings could not only

help those infected with HCV but also the large majority of people who develop diabetes by the interaction of multiple heritable and environmental factors.

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