Diabetes is Associated with Chronic Liver Disease and Liver Cancer in the Adult Population of Puerto Rico

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Objective: Diabetes mellitus (DM) has been proposed as a risk factor for both chronic liver disease (CLD) and for hepatocellular carcinoma (HCC); however, studies among Hispanics are limited. Puerto Rico (PR) has a high prevalence of DM (13%), supporting the need for a better understanding of the public health implications associated with DM in this population. We assessed the association of DM with CLD and with HCC in a population of Puerto Rican adults with health insurance.

Methods: The study sample consisted of 1,040,025 individuals, aged ≥18 years, all covered by the government-run healthcare program in PR, in 2002. The ICD-9 codes for DM, CLD, and HCC were obtained in order to determine the prevalence of these conditions. Logistic regression models were used to determine the association of DM with CLD and with HCC, after adjusting for covariates.

Results: The prevalence of DM was higher in patients with CLD (17%) and those with HCC (18%) than it was in patients without either of these conditions (8% and 7%, respectively). Among women, those with DM were significantly more likely to have CLD than were those without DM (POR: 35-49 yrs: 3.26, 95% CI = 2.12, 5.00; POR: 50-64 yrs: 2.10, 95% CI = 1.63, 2.71; POR: ≥65 yrs: 2.33, 95% CI = 1.67, 3.25). Among men, those with DM were more likely to have CLD than were those without DM; this association was significant among males aged 50-64 (POR: 1.30, 95% CI = 1.03-1.63) and those aged ≥65 yrs (POR: 1.94, 95% CI = 1.35-2.80).

Conclusion: Consistent with other studies, we observed a strong association of DM with CLD and HCC. In order to reduce the burden of these conditions in PR, research and public health efforts should be concentrated on gaining a better understanding of these associations. [*P R Health Sci J 2011;30:132-134*]

Key words: Diabetes, Chronic liver disease, Liver cancer, Puerto Rico

Diabetes mellitus (DM) consists of a heterogeneous group of metabolic diseases characterized by chronic hyperglycemia. It is associated with increased levels of insulin and insulin-like growth factors (IGF), which are potential cancer-promoting factors (1). Some studies have suggested an association between DM and chronic liver disease (CLD), the main risk factor for hepatocellular carcinoma (HCC) (2-4), and DM has been identified as an independent risk factor for HCC (3, 5-7).

Type 2 DM is the fifth-leading cause of death among Hispanics in the United States (3% of total deaths in 2002) (8) and the third-leading cause of death in Puerto Rico (PR) (7.7% of total deaths in 2008) (9). PR has the highest prevalence of self-reported DM (12.9%; 95% CI: 11.8%-14.0%) of all of the states and territories of the US (10). Therefore, the epidemic of DM in our population may further increase the incidence of CLD and HCC, supporting the need for a better understanding of the public health implications associated with DM. Because of the existing need to assess the impact of DM in both PR and US Hispanics, we examined the association of DM with CLD and with HCC in a population of insured adults in PR.

Methods

We performed a cross-sectional study, based on a secondary data analysis, of the data collected from members of the adult population who were enrolled in the government-administered health care plan in 2002. The mid-year population of insured individuals was 1,040,025, representing nearly 27% of Puerto Rico's total population (3,858,806) for the year of 2002. Codes from the Ninth Revision of the International Classification of Diseases (ICD-9) were used to determine disease history (yes/no), which was defined as an individual having at least two medical claims during 2002. The main outcome variables

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included CLD (ICD-9 571, 572.2, 572.4, 572.3, 572.8) and HCC (ICD-9 155.0), while DM (ICD-9 250) was the main independent variable. Potential confounding variables evaluated included age, sex, hepatitis C virus (HCV) infection (ICD-9 070.41, 070.44, 070.51, 070.54, 070.70, 070.71; V02.62), and hepatitis B virus (HBV) infection (ICD-9 070.22, 070.23, 070.32, 070.33, V02.61). Logistic regression models were used to model the crude and covariate-adjusted associations (prevalence odds ratio [POR]) of DM with CLD and HCC. Variables found in bivariate analysis to be associated ($p<0.05$) with both DM and CLD/HCC were included in multivariate logistic regression models. The Wald test was used to assess the presence of interaction in the models. Data were analyzed with the statistical package SPSS version 11 (SPSS Inc., Chicago, IL). This study was approved by the Institutional Review Board of the Medical Sciences Campus, University of Puerto Rico.

Results

The study results showed that the prevalence of CLD was higher among males (0.27%) than it was among females (0.12%), while 0.03% of men and 0.02% of women had HCC (data not shown). The prevalence of DM was 7.3% for men and 7.8% for women. The prevalence of DM was higher both in patients with CLD (17%) and in those with HCC (18%) in comparison with those patients without either of these conditions (8% and 7%, respectively). In bivariate analysis, older adults, males and those with a history of DM, HBV, and HCV were more likely to have CLD. A similar pattern was observed for HCC, with older individuals, males, and those with DM and HCV infection being more likely to have HCC (data not shown).

Sex and age were found to act as effect modifiers of the association between DM and CLD; thus, independent covariate adjusted logistic regression models were considered.

Among women, those with DM were significantly more likely to have CLD than were those without DM (POR: 35-49yrs: 3.26, 95% CI = 2.12, 5.00; POR: 50-64yrs: 2.10, 95% CI = 1.63, 2.71; POR: ≥65+yrs: 2.33, 95% CI = 1.67, 3.25). Among men, those with DM were more likely to have CLD than were those without DM; this association was significant among males aged 50-64 (POR: 1.30, 95% CI = 1.03-1.63) as well as those aged ≥65 (POR: 1.94, 95% CI = 1.35-2.80) (Table 1). DM was also associated with HCC (POR: 1.65, 95% CI = 1.17-2.34), after adjusting for age, sex, and HCV infection (Table 2).

Discussion

Consistent with previous studies performed in other populations (2-6, 11), this study evidenced strong associations of DM with CLD and with HCC. Although the exact mechanisms of these associations are not completely clear, it is known that the stimulation of IGF receptors promotes chronic inflammation, liver injury, and tumorigenesis (3-4, 7, 12).

One of the strengths of the study is that our insured population represented nearly one-third of the total population of Puerto Rico in 2002. Among the study's limitations were that potential miscoding of selected study conditions by providers and the fact that disease status was determined by the presence of at least two claims (ICD-9) in the database may have led to the occasional misclassification of disease status. This source of information bias in our study is likely to be non-differential, thus biasing our results towards the null hypothesis. Because of the limited use of ICD coding by providers for certain conditions (such as obesity, alcoholism, and tobacco use), this study was unable to provide a full evaluation of the potential confounding effects of these variables on the associations of interest. Thus, the possibility of residual confounding cannot be excluded.

Our results support the view that public health efforts should be concentrated on better understanding the effects of DM on CLD and on HCC in order to reduce the burden of these conditions in our population. Longitudinal studies that can further elucidate these associations are highly warranted, as the temporal relationship between DM, CLD, and HCC needs to be established in this Hispanic population. This is essential to elucidate the causal relationships between DM, CLD and HCC.

Table 1. Logistic regression model for the association between DM and CLD*†, by sex and age group‡.

Sex	Age group (years)	Adjusted POR (95% CI)
Females	35-49	3.26 (2.12 - 5.00)
	50-64	2.10 (1.63 - 2.71)
	≥65	2.33 (1.67 - 3.25)
Males	35-49	1.29 (0.88 - 1.91)
	50-64	1.30 (1.03 - 1.63)
	≥65	1.94 (1.35 - 2.80)

*A Wald test showed a significant interaction ($p<0.05$) of sex and age; thus, independent regression models were done for males and females by age group.
†Adjusted by HCV status.
‡Age group 18-34 excluded from this analysis because of small numbers.

Table 2. Logistic regression model for the association between DM and HCC‡.

Covariates	Adjusted POR (95% CI)
Diabetes	
+	1.65 (1.17-2.34)
-	1.00
Sex	
Female	1.00
Male	2.11 (1.62-2.76)
Age	
35-49	1.00
50-64	2.67 (1.79-3.97)
≥65	3.82 (2.58-5.65)
HCV	
+	26.06 (10.62-63.94)
-	1.00

‡Age group 18-34 excluded from this analysis because of small numbers.

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Resumen

Objetivo: La diabetes se ha propuesto como un factor de riesgo para la enfermedad crónica del hígado (CLD, por sus siglas en inglés) y el cáncer hepatocelular (HCC, por sus siglas en inglés), sin embargo los estudios en hispanos son limitados. Dada la alta prevalencia de diabetes en Puerto Rico (PR) (13%), en este estudio se evaluó la asociación de la diabetes con CLD y HCC en una población de adultos con cubierta médica en PR. Métodos: La población del estudio consistió de 1,040,025 adultos, ≥18 años, cubiertos bajo el plan de salud gubernamental durante el 2002. Los códigos del ICD-9 para diabetes, CLD y HCC fueron utilizados para determinar la prevalencia de estas condiciones. Modelos de regresión logística fueron utilizados para determinar la asociación de la diabetes con CLD y HCC, luego de ajustar por variables de interés. Resultados: La prevalencia de diabetes fue mayor en pacientes con CLD (17%) y HCC (18%) que en pacientes sin estas condiciones (8% y 7%, respectivamente). Entre las mujeres, aquellas con diabetes tenían mayor posibilidad de tener CLD que aquellas sin diabetes (POR: 35-49 años: 3.26, 95% CI = 2.12, 5.00; POR: 50-64 años: 2.10, 95% CI = 1.63, 2.71; POR: ≥65 años: 2.33, 95% CI = 1.67, 3.25). Entre los hombres se observó un patrón similar en aquellos de 50-64 años (POR: 1.30, 95% CI = 1.03-1.63) y aquellos ≥65 años (POR: 1.94, 95% CI = 1.35-2.80). La diabetes también estuvo asociada al HCC (OR = 1.65, 95% CI = 1.17-2.34). Conclusión: Consistente con otros estudios, observamos una fuerte asociación de la diabetes con CLD y el HCC. Para reducir la carga de estas condiciones en PR, esfuerzos de investigación y salud pública deben ser concentrados en entender mejor estas asociaciones.

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