HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Diabetes and Prediabetes in Patients With Hepatitis B Residing in North America

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Diabetes is associated with liver disease progression and increased hepatocellular carcinoma risk, but factors associated with diabetes in patients with chronic hepatitis B virus (HBV) infection in North America are unknown. We aimed to determine factors predictive of diabetes and impaired fasting glucose (IFG) in a large HBV-infected multiethnic cohort. Adults with chronic HBV not receiving antiviral therapy were enrolled from 21 centers in North America. Diabetes was defined by history/medication use or fasting glucose ≥126 mg/dL and IFG as fasting glucose 100-125 mg/dL. Of 882 patients included, 47.2% were female, 71.3% Asian, 83.7% foreign born, median age was 44 years, and median body mass index BMI 24.3 kg/m^2. In this cohort, 26.0% were hepatitis B envelope antigen (HBeAg) positive, 43.9% had HBV DNA ≥20,000 IU/mL, and 26.7% alanine aminotransferase (ALT) ≥2× upper limit of normal (≥40 U/L women, ≥60 U/L men). Overall, 12.5% had diabetes and 7.8% IFG. The combined prevalence of diabetes or IFG was highest among blacks (36.7%) and those either born in the United States/Canada or foreign born with migration >20 years ago (25.5%). Obesity (odds ratio [OR]: 2.13), hyperlipidemia (OR, 4.13), hypertension (OR, 3.67), high ALT level (OR, 1.86), and family history of diabetes (OR, 3.43) were associated with diabetes. Factors associated with IFG were obesity (OR, 4.13) and hypertension (OR, 3.27), but also HBeAg positivity (OR, 0.39). Recent migration was negatively associated with diabetes among non-Asians (OR, 0.30). *Conclusions*: Diabetes is more prevalent in HBV-infected North American adults than the general population and is associated with known metabolic risk factors and liver damage, as determined by ALT levels. Among the foreign born, longer duration of North America residence predicted diabetes risk in non-Asians. These results highlight the opportunities for interventions to prevent diabetes especially among at-risk ethnic groups with HBV. (HEPATOLOGY 2015;62:1364-1374)

An estimated 1.25 million individuals in the United States are chronically infected with hepatitis B virus (HBV) and approximately 43,000 new infections occur annually.[1,2] Recent data suggest that the number of foreign-born individuals with chronic HBV living in the United States may be greater than previously reported, and the actual number of persons with chronic HBV infection may be as high as 2.2 million.[3] Chronic HBV infection is associated with a risk of progression to cirrhosis, liver failure, and development of hepatocellular carcinoma (HCC).[4] As such, HBV represents a significant public health burden in North America. The majority of HBV-infected individuals in North America are foreign born and have emigrated from endemic regions such as Asia and the Pacific Islands and Africa.[3] A growing body of evidence indicates that the observed rise in the incidence of obesity in North America and its associated syndromes, especially diabetes and metabolic syndrome, may contribute to the negative consequence of HBV disease.[5,6] For example,

Abbreviations: ADA, American Diabetes Association; ALT, alanine aminotransferase; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HBeAg, hepatitis B envelope antigen; HBRN, Hepatitis B Research Network; HBsAg, hepatitis B surface antigen; HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IFG, impaired fasting glucose; OR, odds ratio; ULN, upper limit of normal.

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Received February 1, 2015; accepted August 4, 2015.

Additional Supporting Information may be found in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/hep.28110/suppinfo.

these conditions have been associated with increased liver inflammation,[7] progression of liver fibrosis,[8-10] and increased mortality in the setting of HBV infection.[11] Persons with diabetes also have higher prevalence of hepatitis B than the general population, and HBV testing and vaccination in susceptible individuals is recommended in diabetics.[12] Moreover, diabetes is independently associated with an approximately 2-fold increase in risk of liver cancer, compared to nondiabetics, and this risk increases by 100-fold in the presence of combined diabetes and obesity among those infected with hepatitis B or C infection.[13] This suggests that viral and metabolic effect may accelerate progression of liver disease and increase liver cancer risk. Therefore, prevention and control of diabetes may contribute to improving HBV disease outcomes.

Considering the epidemic of diabetes, appropriate screening and treatment of prediabetic states, such as impaired fasting glucose (IFG), has importance in the control of diabetes. Early identification of prediabetes and intervention with lifestyle modification and/or pharmacological therapy is currently recommended.[14] IFG is exceedingly prevalent in North America, affecting approximately 37% of adults age 20 years and older.[15] The limited information to date, predominantly from HBV endemic regions, shows that prevalence of diabetes among persons with chronic HBV infection varies among countries and ranges from 6% to 14%.[16-19] In a study using data from the National Health and Nutrition Examination Survey III where only approximately 0.4% of the 15,866 subjects had chronic hepatitis B, prevalence of diabetes was reported as $7.0 \pm 4.8\%$.[11] There is even less information on the prevalence of prediabetes. In one study, approximately 26% of Nigerians with chronic HBV had IFG.[20] The reported factors associated with abnormalities of glucose metabolism have included both host and viral factors.[16,20,21] However, these studies may not be applicable to the North American HBV-infected population owing to greater ethnic diversity as well as differences in global prevalence of obesity and metabolic abnormalities.

Given the paucity of data and the high prevalence of metabolic abnormalities in North America, we assessed the prevalence of diabetes and IFG as well as the relationship between host and viral factors and abnormalities of glucose metabolism in a large racially diverse North American cohort with chronic HBV infection.

Patients and Methods

This is a cross-sectional study of patients enrolled within the Hepatitis B Research Network (HBRN) Adult Cohort Study from January 14, 2011 to July 23, 2013. The HBRN Cohort Study is a prospective study of hepatitis B surface antigen (HBsAg)-positive adult patients, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, and comprises 21 adult liver centers in the United States and in Toronto, Canada. Details of the HBRN and the adult cohort study had been described previously.[22] The HBRN Adult Cohort Study enrolled HBsAg-positive persons greater than 18 years of age who did not have a history of hepatic decompensation, HCC, solid organ or bone marrow transplantation or human immunodeficiency virus (HIV) coinfection, and who were not receiving antiviral therapy. For this study, participants with acute

The HBRN was funded by a U01 grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to the following investigators: Lewis R. Roberts, M.B., Ch.B., Ph.D. (DK 082843); Anna Suk-Fong Lok, M.D. (DK082863); Steven H. Belle, Ph.D., MScHyg (DK082864); Kyong-Mi Chang, M.D. (DK082866); Michael W. Fried, M.D. (DK082867); Adrian M. Di Bisceglie, M.D. (DK082871); William M. Lee, M.D. (U01 DK082872); Harry L.A. Janssen, M.D., Ph.D. (DK082874); Daryl T.-Y. Lau, M.D., M.P.H. (DK082919); Richard K. Sterling, M.D., M.Sc. (DK082923); Steven-Huy B. Han, M.D. (DK082927); Robert C. Carithers, M.D. (DK082943); Norah A. Terrault, M.D., M.P.H. (U01 DK082944); an interagency agreement with NIDDK: Lilia M. Ganova-Raeva, Ph.D. (A-DK-3002-001) and support from the intramural program, NIDDK, National Institutes of Health (NIH): Marc G. Ghany, M.D. Additional funding to support this study was provided to Kyong-Mi Chang, M.D., the Immunology Center (NIH/NIDDK Center of Molecular Studies in Digestive and Liver Diseases P30DK50306, NIH Public Health Service Research Grant M01-RR00040), Richard K. Sterling, M.D., M.Sc. (UL1TR000058, NCATS [National Center for Advancing Translational Sciences], NIH), Norah A. Terrault, M.D., M.P.H. (CTSA grant no: UL1TR000004), Michael W. Fried, M.D. (CTSA grant no.: UL1TR001111), and Anna Suk-Fong Lok (CTSA grant no.: UL1RR024986). Additional support was provided by Gilead Sciences, Inc., and Roche Molecular Systems by a CRADA through the NIDDK.

The HBRN: Hepatitis B Research Network members are listed in the Appendix to this article.

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DOI 10.1002/hep.28110

Potential conflict of interest: Dr. Chung received grants from Gilead and Bristol-Myers Squibb. Dr. Lisker-Melman is on the speakers' bureau for Gilead, Simply Speaking, and AbbVie. Dr. Sanyal consults for and received grants from Gilead, Echosens-Sandhill, Ikaria, Salix, Takeda, Novartis, and Galectin. He consults for Abbott, Genentech, GenFit, Immuron, Intercept, Merck, Norgine, Roche, Nimbus, Nitto Denko, Sequana, and Bristol-Myers Squibb. He received grants from Conatus and Astellas and received royalties from UpToDate.

HBV infection, or were pregnant, or did not have known baseline diabetes status or fasting glucose values within 6 months of the baseline visit were excluded. American Diabetes Association (ADA) recommends diagnosis of diabetes or prediabetes based on hemoglobin A1C or plasma glucose—fasting levels or 2-hour value after a 75-g oral glucose tolerance test.[23] Hemoglobin A1C and oral glucose tolerance test were not performed in the HBRN Cohort Study. Type 2 diabetes (referred to as diabetes throughout) was therefore defined as a known history of diabetes or current use of antidiabetic medications or fasting glucose $\geq$126 mg/dL.[24] IFG was defined as fasting glucose levels of 100-125 mg/dL.[24]

All protocols were approved by the HBRN Steering Committee and the Institutional Review Boards (Research Ethics Board in the case of the Toronto site) of the participating sites, and all participants provided written informed consent.

Statistical Analysis. Descriptive statistics included median and range and mean $\pm$ standard deviation, as appropriate. Overweight was defined as body mass index (BMI) 23-27.5 kg/m^2 if Asian and 25-30 kg/m^2 for all other racial groups, and obesity was defined as BMI $>$27.5 kg/m^2 if Asian and $>$30 kg/m^2 for all other racial groups.[25] High-risk waist circumference was defined as $\geq$88 cm for women ($\geq$80 for Asian women) and $\geq$102 cm for men ($\geq$90 cm for Asian men).[26] Upper limit of normal (ULN) for alanine aminotransferase (ALT) was 30 U/L for males and 20 U/L for females.[2] History of hypertension and hyperlipidemia was obtained by clinical history or use of medications for these conditions. Aspartate aminotransferase (AST) to platelet ratio index (APRI) score was used to assess significant liver fibrosis and defined as (AST levels divided by its ULN)/platelet counts (10^9/L) $\times$ 100.[27] Alcohol consumption was graded as none or minimal ($<$1 drink per month), moderate ($\leq$4 drinks/day or 14/week in men, $\leq$3 drinks/day, or 7/week in women), or heavy (not moderate).[28]

The nonparametric Kruskal-Wallis test was used to compare continuous variables, and the chi-square test or the Fisher's exact test, when needed, were used to compare categorical variables. Logistic regression models were used to estimate the adjusted association between baseline variables and presence of diabetes and/or IFG at baseline. For variables with missing values, the missing values were replaced by an arbitrary numeric value (0) and a separate indicator variable (0/1) was included in the model, where the numerical value of 1 represented the records with missing values.[29] Through this technique, all records were kept in the regression models. SAS softare (version 9.3; SAS Institute Inc., Cary, NC) was used for all analyses.

Results

Of the total of 1,559 consecutive and nonpregnant patients with chronic HBV infection enrolled in the HBRN Adult Cohort Study during the study period, 677 patients with no known history of diabetes were excluded because of unavailable fasting glucose levels to ascertain diabetes or prediabetes status (Fig. 1). The remaining 882 were included in this study. The characteristics of patients who were (n = 882) or were not (n = 677) included were similar with respect to mean age (43.9 vs. 43.2; $P = 0.2$), sex (47.2% female vs. 46.4% female; $P = 0.8$), and race (white 10.9% vs. 10.8%, black 14.5% vs. 14.3%, Asian 71.3% vs. 70.6%, and Latino/other racial group 3.3% vs. 4.3%; $P = 0.8$).

Prevalence of Diabetes and IFG. Overall, 110 patients (12.5%) had diabetes, 69 (7.8%) had IFG, and 703 (79.7%) had normal glucose levels. Patients with normal glucose levels were significantly (all $P < 0.0001$) younger, had smaller waist circumference, lower BMI, as well as lower prevalence of hypertension and hyperlipidemia than those with glucose abnormalities (IFG or diabetes; Supporting Table 1). Among persons with glucose abnormalities, those with diabetes were significantly older ($P = 0.007$) and had higher prevalence of hypertension ($P = 0.003$), hyperlipidemia ($P < 0.001$), and family history of diabetes ($P < 0.001$) than those with IFG.

Table 1 summarizes the prevalence of glucose abnormalities by various cohort characteristics. Seven hundred thirty-eight (83.7%) patients were foreign born. The main countries of origin among foreign-born Asians were China (41.4%) and Vietnam (22.1%), whereas Somalia (44.7%) was the main country of origin among foreign-born blacks. The prevalence of diabetes was highest among blacks and lowest among Asians (23.4% vs. 9.5%; $P < 0.0001$; Fig. 2). The prevalence of IFG was also highest among blacks (13.3%) and was nearly double that of other racial groups. The combined prevalence of diabetes or IFG was higher among those who were born in the United States/Canada or foreign born with more than 20 years of migration to the United States/Canada, compared to those who were foreign born with a shorter duration of migration (25.5% vs. 13.4%; $P < 0.0001$). The prevalence of diabetes was also higher among those with significant liver fibrosis or cirrhosis defined as APRI score $>$1.5 (20.5% vs. 11.5%; $P = 0.1$) and those with elevated ALT levels (16.3% vs. 10.5%; $P = 0.05$), but these differences were not statistically significant. Even after stratification by age, prevalence of glucose abnormalities was significantly higher in the groups with higher ALT levels ($P = 0.04$; Fig. 3A).

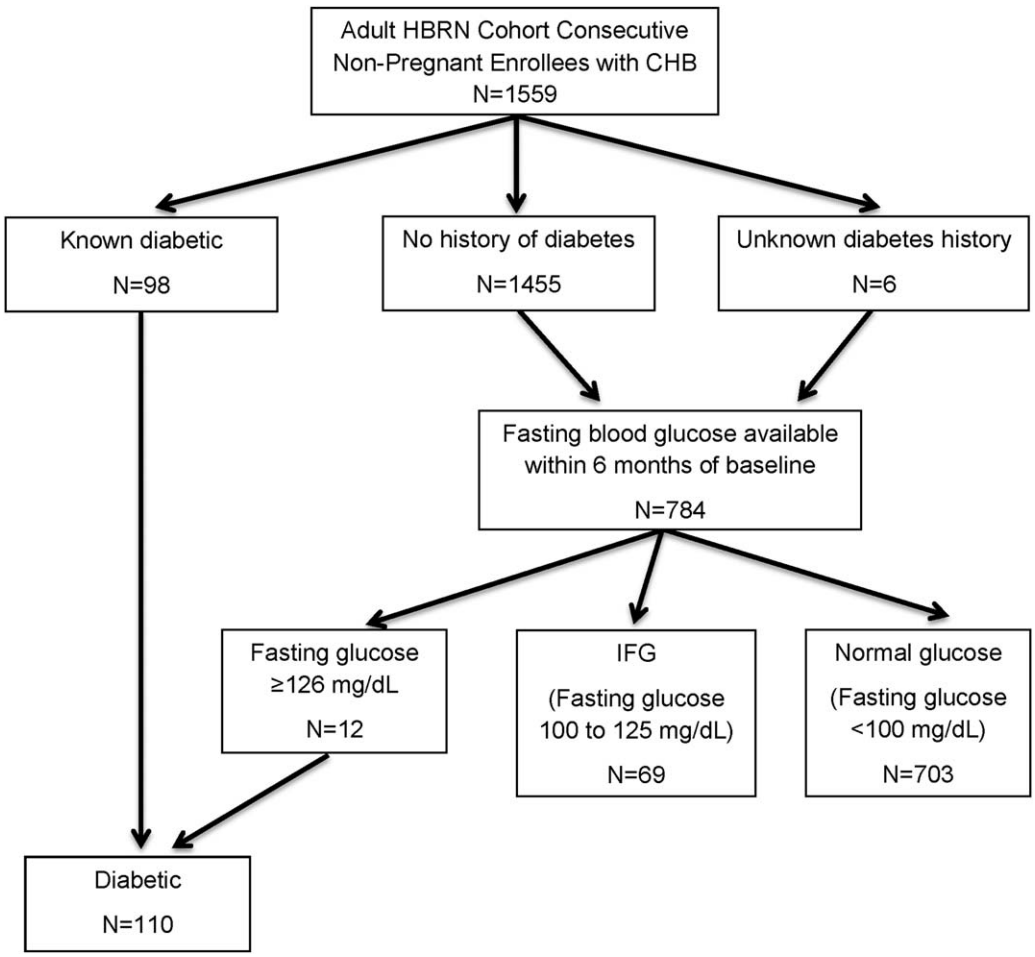

Fig. 1. Schema of patient selection.

Although the overall rate of diabetes was higher in hepatitis B envelope antigen (HBeAg)-negative than in HBeAg-positive patients (13.4% vs. 7.8%), when stratified by age, the overall prevalence of glucose abnormalities (IFG vs. diabetes vs. normal glucose) in HBeAg-positive and HBeAg-negative patients was not different ($P = 0.47$; Fig. 3B). Similar to observations in the general population, the prevalence of diabetes was lower in those with moderate alcohol consumption than those with a history of heavy or no alcohol intake (8.8% vs. 16.9% or 13.1%, respectively), although this did not reach statistical significance ($P = 0.5$).

Relationship Between Host and HBV-Related Factors and Abnormalities of Glucose Metabolism. In multivariable logistic regression models that controlled for age, gender, and race, patients with high ALT ($\geq 2\times$ ULN) levels were nearly 2 times more likely to have diabetes, compared with those with lower ALT (odds ratio [OR]: 1.86; 95% confidence interval [CI]: 1.05-3.30). HBV viral load or HBeAg status was not associated with diabetes in the adjusted model. Additional predictors of diabetes included obesity (OR, 2.13; 95% CI: 1.01-4.49), history of hyperlipidemia (OR, 4.13; 95% CI: 2.33-7.32), history of hypertension (OR, 3.67; 95% CI: 2.05-6.57), and family history of diabetes (OR, 3.43; 95% CI: 2.00-5.88; Table 2). On the other hand, whereas obesity and history of hypertension predicted IFG, HBeAg-positive status (OR, 0.39; 95% CI: 0.16-0.98) was negatively associated with IFG. On further analysis (data not shown), the negative association between HBeAg status and IFG did not vary with age ($P = 0.23$). Given that only 18.7% of patients had a known estimated duration of HBV infection that differed from age (owing to assumed nonvertical transmission as the mode of infection), duration of HBV infection was not included in the multivariable models.

Impact of Duration of Immigration to United States or Canada on Diabetes Prevalence in Patients With Chronic HBV Infection. Being a recent immigrant, defined as having moved to the United States or Canada in the last 20 years, had a strong negative association with diabetes (OR, 0.29; 95% CI: 0.18-0.46; $P < 0.0001$) in unadjusted analysis. However, after adjustment for age, family history of diabetes, BMI, and

Table 1. Prevalence of Normal Glucose Levels, IFG, and Diabetes Among Various Host and Viral Patient Characteristics

	Normal Glucose Levels	IFG	Diabetes	*P* Value*
HBV-Related Characteristics				
ALT level, %				
≥2× ULN (n = 233)	77.3	6.4	16.3	0.05
<2× ULN (n = 639)	81.1	8.5	10.5	
HBV-DNA level, IU/mL %				**0.02**
≥20,000 (n = 380)	83.7	5.3	11.1	
<20,000 (n = 485)	76.9	9.9	13.2	
HBeAg status, %				**0.0002**
Positive (n = 218)	89.4	2.8	7.8	
Negative (n = 621)	77.1	9.5	13.4	
Fibrosis by APRI score, %				0.1
>1.5 (n = 39)	76.9	2.6	20.5	
≤1.5 (n = 775)	80.0	8.5	11.5	
Estimated duration of HBV infection, years				0.04
<20 (n = 103)	74.8	14.6	10.7	
20-39 (n = 260)	86.2	6.9	6.9	
≥40 (n = 206)	78.6	8.7	12.6	
Host-Related Characteristics				
Age category, %, years				**<0.0001**
<30 (n = 151)	94.7	4.0	1.3	
30-49 (n = 424)	85.4	6.8	7.8	
≥50 (n = 307)	64.5	11.1	24.4	
Sex, %				**0.03**
Female (n = 416)	83.4	5.8	10.8	
Male (n = 466)	76.4	9.7	13.9	
Race, %				**<0.0001**
White (n =96)	77.1	6.3	16.7	
Black (n = 128)	63.3	13.3	23.4	
Asian (n = 629)	83.3	7.2	9.5	
Other (n = 29)	82.8	3.4	13.8	
Continent of birth, %				**0.0006**
Africa (n = 87)	73.6	14.9	11.5	
Asia (n = 596)	83.1	7.2	9.7	
Europe (n = 34)	88.2	2.9	8.8	
North America (n = 156)	69.9	7.7	22.4	
South America (n = 6)	66.7	0	33.3	
Australia (n = 2)	50.0	0	50.0	
Birth and migration status, %				**<0.0001**
U.S./Canada birth (n = 144)	70.1	8.3	21.5	
Foreign born and migrated >20 years (n = 268)	76.9	7.5	15.7	
Foreign born and migrated ≤20 years (n = 426)	86.6	7.5	5.9	
Foreign born, but unknown migration time (n = 43)	62.8	11.6	25.6	
Waist circumference category adjusted for race and sex, %, cm				**0.01**
High risk (n = 290)	78.6	8.6	12.8	
Low risk (n = 435)	86.7	6.0	7.4	
Race-adjusted BMI category, %				**<0.0001**
Normal (n = 341)	90.3	3.5	6.2	
Overweight (n = 345)	80.3	8.4	11.3	
Obese (n = 170)	59.4	15.3	25.3	
Alcohol consumption in the previous 12 months, %				0.5
None (n = 650)	79.4	7.5	13.1	
Moderate (n = 170)	82.9	8.2	8.8	
Heavy (n = 59)	76.3	6.8	16.9	
Hypertension history, %				**<0.0001**
Yes (n = 184)	45.7	15.8	38.6	
No (n = 693)	88.7	5.8	5.5	
Hyperlipidemia history, %				**<0.0001**
Yes (n = 133)	44.4	10.5	45.1	
No (n = 741)	85.8	7.4	6.7	
Family history of diabetes, %				**<0.0001**
Yes (n = 326)	69.6	8.0	22.4	
No (n = 556)	85.6	7.7	6.7	

*P values are for all group comparison and $P < 0.05$ (two-sided) is considered statistically significant. Bolded P values < 0.05.

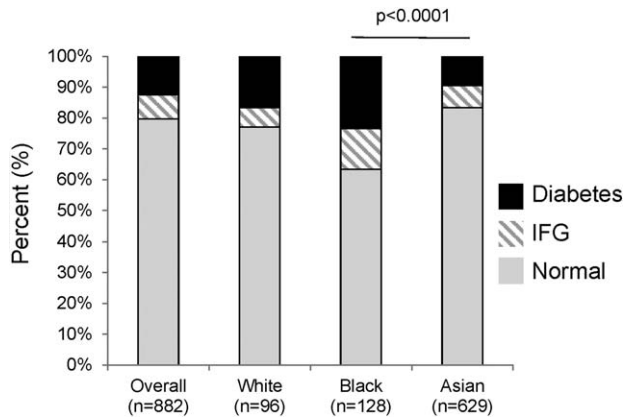

Fig. 2. Prevalence of normal glucose, IFG, and diabetes among various racial groups.

hypertension, all of which are known risk factors for diabetes, recent immigrant status was no longer associated with diabetes (OR, 0.64; 95% CI: 0.35-1.17; $P = 0.15$). We identified race to be an effect modifier. After controlling for predictors that were generally associated with diabetes, recent migration had a significant negative association with diabetes, with an estimated 70% reduction in the odds of diabetes among non-Asians (OR, 0.3; 95% CI: 0.10-0.94; $P = 0.04$), but not among Asians (OR, 1.09; 95% CI: 0.52-2.30; $P = 0.82$). The multivariable models are presented separately for Asian and non-Asian patients in Table 3.

Discussion

Type 2 diabetes represents a major public health burden owing to its rising prevalence worldwide.[30] Because patients with diabetes have higher prevalence of HBV infection, screening and treatment of prediabetes and diabetes are especially relevant in this population given that impaired glucose metabolism has been shown to promote liver fibrosis[8-10] and increase the risk of HCC.[4] This study evaluated the prevalence of glucose

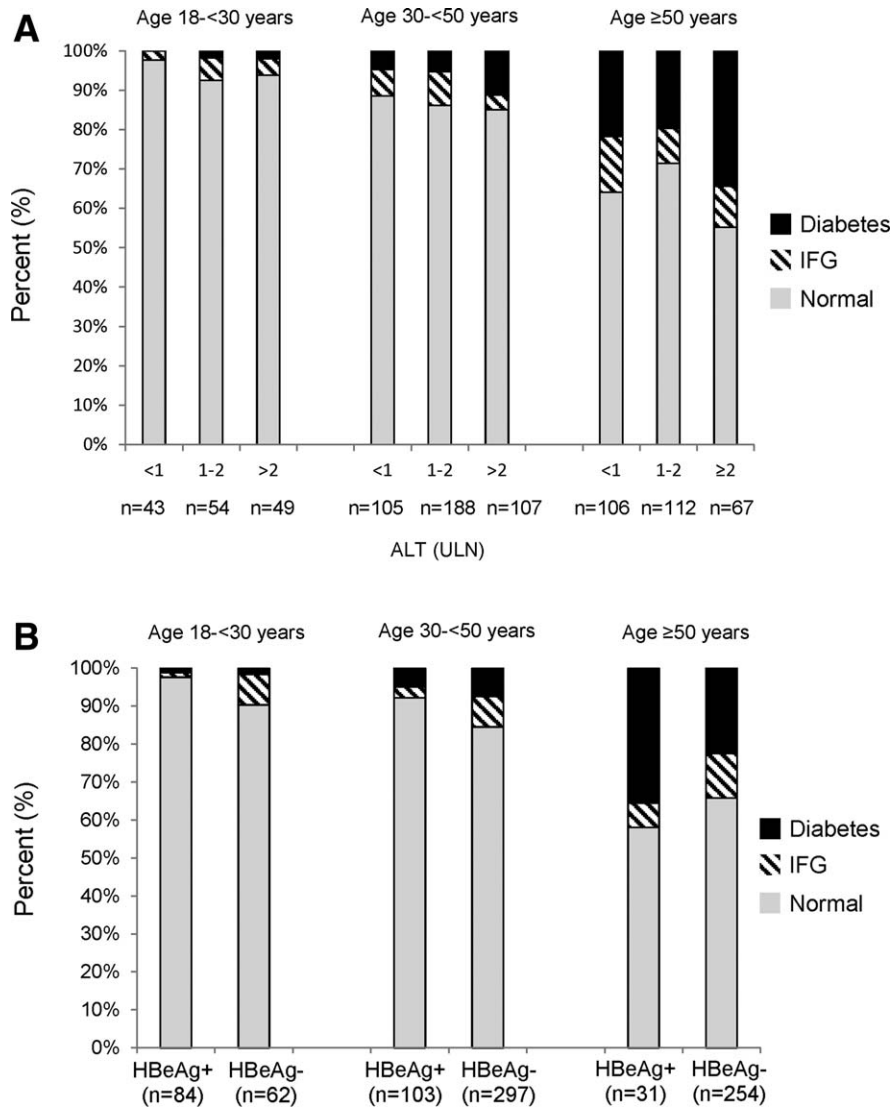

Fig. 3. (A) Prevalence of normal glucose, IFG, and diabetes according to baseline ALT: normal, 1-2× ULN, and >2× ULN, stratified by age group (overall $P = 0.04$). (B) Prevalence of normal glucose, IFG, and diabetes in $HBeAg^+$ and in HBeAg-negative patients, stratified by age group (overall $P = 0.47$).

Table 2. Factors Independently Associated With IFG and Diabetes Among Patients With Chronic HBV

	IFG		Diabetes	
Predictors	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Age (per decade)	1.23 (0.95, 1.59)	0.11	1.83 (1.41, 2.39)	**<0.0001**
Male sex	1.64 (0.93, 2.90)	0.06	1.43 (0.84, 2.45)	0.19
Race (vs. white)				
Black	2.79 (0.97, 8.00)	0.06	1.68 (0.69, 4.10)	0.25
Asian	1.94 (0.74, 5.06)	0.18	0.92 (0.42, 2.00)	0.83
Other	0.63 (0.07, 5.92)	0.69	0.63 (0.13, 2.97)	0.56
Race-adjusted BMI categories (vs. normal)				
Overweight	1.89 (0.92, 3.87)	0.08	1.09 (0.55, 2.14)	0.81
Obese	4.02 (1.85, 8.71)	**0.0004**	2.13 (1.01, 4.49)	**0.048**
Hyperlipidemia history			4.13 (2.33, 7.32)	**<0.0001**
Hypertension history	3.00 (1.60, 5.64)	**0.0006**	3.67 (2.05, 6.57)	**<0.0001**
Diabetes family history			3.43 (2.00, 5.88)	**<0.0001**
High ALT (≥2× ULN)			1.86 (1.05, 3.30)	**0.03**
HBeAg-positive status	0.39 (0.16, 0.98)	**0.044**		

Bolded *P* values < 0.05.

abnormalities and the associated factors in a large cohort of multiethnic HBV-infected persons residing in the United States and Canada. We demonstrated that nearly one quarter of this cohort had diabetes (13%) or prediabetes (8%). Current estimates of prevalence of diabetes in U.S. and Canadian adults are 9% and 8%, respectively,[15,31] and approximately 37% of the U.S. population 20 years or older has IFG,[15] suggesting that diabetes was more prevalent, but IFG less prevalent, in our HBV cohort compared to the general population. However, the racial/ethnic composition of the HBRN cohort is markedly different from that of the general population in the United States or Canada. We also showed a significant association between liver damage as determined by ALT levels and diabetes in patients with chronic HBV infection, suggesting that lowering ALT levels with antiviral therapy or weight loss, as well as effective diabetes management, may be a potentially important means of decreasing the risk of liver disease progression in this population.

Previous studies have suggested that the inflammatory milieu associated with chronic viral infections may influence hepatic glucose sensitivity and increase insulin resistance.[32] Liver inflammation has also been shown to be a risk factor for prediabetes in the setting of hepatitis C infection.[33] The finding that serum ALT was associated with diabetes provides support for the hypothesis that active necroinflammation in the liver, whether HBV related or not, predisposes to hyperglycemia, perhaps through oxidative or endoplasmic reticulum//ER stress.[34] Alternatively, the elevated ALT among diabetics may reflect concurrent fatty liver, though liver biopsy or standardized imaging data were not available to confirm this diagnosis. In this cross-sectional analysis, we cannot discern what is cause and effect, but with longitudinal follow-up of this cohort, the contribution of HBV-related liver damage to diabetes/prediabetes risk can be studied and the impact of glucose abnormalities on liver disease progression can be evaluated.

Table 3. Factors Independently Associated With Diabetes Among Asians Versus Non-Asians With Chronic HBV

	Non-Asian N = 229		Asian N = 584	
Predictors	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Age (per decade)	1.71 (1.09, 2.64)	**0.02**	1.87 (1.33, 2.64)	**0.0004**
Male sex	2.02 (0.81, 5.02)	0.13	1.17 (0.58, 2.37)	0.66
Race-adjusted BMI categories (vs. normal)				
Overweight	0.96 (0.27, 3.45)	0.95	1.04 (0.45, 2.41)	0.92
Obese	3.04 (0.89, 10.3)	0.08	1.61 (0.57, 4.54)	0.37
Foreign born and migrated ≤20 years ago (vs. U.S./Canada birth or foreign born and migrated >20 years ago)	0.30 (0.10, 0.94)	**0.04**	1.09 (0.52, 2.30)	0.82
Hyperlipidemia history	2.75 (1.07, 7.05)	**0.04**	6.14 (2.87, 13.1)	**<0.0001**
Family history of diabetes	3.83 (1.54, 9.56)	**0.004**	2.68 (1.32, 5.47)	**0.007**
Hypertension history	3.40 (1.32, 8.76)	**0.01**	3.78 (1.74, 8.24)	**0.0008**
High ALT (≥2× ULN)	2.30 (0.82, 6.47)	0.11	1.20 (0.56, 2.57)	0.63

Bolded *P* values < 0.05.

Although no viral specific factors were associated with diabetes, HBeAg status was negatively associated with IFG when controlling for age. The significance of this finding is unclear, but the confidence interval around the estimate associated with HBeAg status was wide and reflects some degree of uncertainty about the estimated effect. HBV-DNA levels were not independently associated with diabetes or IFG. These observations suggest that whereas HBV-DNA levels are predictive of clinical outcomes, such as hepatic cirrhosis or HCC,[35,36] they do not appear in and of themselves to be associated with development of diabetes or diabetes risk. Similarly, in a recent study of a large, population-based Alaska Native cohort with over 20 years of follow-up, presence of HBV infection did not have an effect on diabetes development.[21] Instead, our results suggest that diabetes is more closely linked to host factors than to viral factors.

Not surprisingly, diabetes was more prevalent among older persons and those with other metabolic risk factors, specifically higher BMI and waist circumference, hypertension, dyslipidemia, and family history of diabetes. Indeed, the ADA guidelines for prevention of type 2 diabetes recommends that patients with prediabetes be referred to an intensive diet and physical activity behavioral counseling program targeting loss of 7% body weight and metformin therapy may also be considered, especially for those with BMI>35 kg/m^2, age <60 years, and previous history of gestational diabetes.[23] Importantly, we also identified significant racial-ethnic differences in the prevalence of diabetes and prediabetes in the HBV population. The lowest prevalence was noted among Asians and highest among blacks. Overall, birth status or duration of migration on its own was not an independent predictor of diabetes or IFG. However, we found a strong association between duration of time in the United States/Canada and risk of diabetes among foreign-born non-Asians, the majority of whom were of African origin. Duration of migration did not seem to significantly influence risk of diabetes in Asians, most of whom were of Chinese origin. This finding is similar to some previous studies of Chinese Asian population that also did not show a significant influence of length of migration on diabetes risk.[37] This suggests that environmental influences (primarily dietary) may be contributing to higher diabetes risk among some foreign-born and predisposed populations, but not others. Whereas assimilation and migration duration among at-risk immigrant population has been shown to be associated with higher prevalence of diabetes,[38] this has not been consistently observed.[39] This is likely owing to potential differences in acculturation and assimilation among different immigrant populations and the complexity of the relationship between immigration, acculturation, and adverse health outcomes.

There are recognized limitations of this study. Because the racial and potentially age distribution of HBRN cohort is different from the general population in the United States and Canada, it is not possible to directly compare the prevalence of IFG/diabetes to the general population. Owing to its cross-sectional nature, the temporal relationship between diabetes/prediabetes and the metabolic and viral factors could not be assessed. Indeed, the dynamic nature of chronic HBV infection with varying periods of high necroinflammatory activity that may influence diabetes risk over time were not captured. Additionally, fibrosis stage was determined by indirect noninvasive tests (APRI) and may have underestimated the proportion of patients with cirrhosis, the latter a risk factor for diabetes/prediabetes. There are known limitations to either A1C or plasma glucose values to define diabetes/prediabetes, and the definition used may impact their reported prevalence in populations studied. In the HBRN cohort study, oral glucose tolerance test or hemoglobin A1C was not performed and baseline fasting glucose level was used for diagnosis of IFG and previously undiagnosed diabetes. Use of A1C may result in potentially higher reported prevalence of prediabetes,[40] but one-third fewer cases of undiagnosed diabetes compared to fasting plasma glucose criteria, whereas use of oral glucose tolerance test may diagnose more people with diabetes than A1C or fasting glucose cutpoints.[23] The strengths of this study include the large sample size, diverse racial-ethnic population, and detailed information on metabolic cofactors.

In summary, diabetes and prediabetes are prevalent among HBV-infected patients living in the United States and Canada. Among the foreign-born HBV-infected population, who account for the majority of HBV infections in the United States and Canada, we found duration of residence in the United States/Canada to be a predictor of diabetes/prediabetes risk, but only among non-Asians. Importantly, in addition to known metabolic risk factors, diabetes is associated with elevated ALT, but not HBV viral level, in patients with chronic HBV infection. The results of our study provide a basis for education and interventions to prevent and better manage diabetes in HBV-infected patients. This is an important objective, given that diabetes is expected to further increase the risk of HBV-related cirrhosis and HCC. Moreover, our finding suggests a potential role for preventing diabetes through reduction in ALT and liver damage with antiviral therapy or preventing liver disease progression through diabetes management,

weight loss, and reduction in liver damage. These hypotheses warrant further study.

Acknowledgment: In addition to the authors, the HBRN would like to acknowledge the contributions of the following: Harvard Consortium: Nezam Afdhal, M.D., Asad Javaid, M.B.B.S., Jianghe Niu, Johanna Han, Imad Nasser, M.D. (Beth Israel Deaconess Medical Center, Boston, MA). Minnesota Alliance for Research in Chronic Hepatitis B: Alisha C. Stahler, Linda Stadheim, R.N. (Mayo Clinic Rochester, Rochester, MN), Mohamed Hassan, M.D. (University of Minnesota, Minneapolis, MN). Saint Louis Midwest Hep B Consortium: Debra L. King, R.N. (Saint Louis University School of Medicine, St Louis, MO) Rosemary A. Nagy, M.B.A., R.D., L.D. (Washington University, St. Louis, MO). University of Toronto Consortium: Victor Lo, M.A.Sc. (Toronto Western & General Hospitals, Toronto, Ontario, Canada), Danie La, R.N. (Toronto Western & General Hospitals, Toronto, Ontario, Canada), Lucie Liu (Toronto Western & General Hospitals, Toronto, Ontario, Canada). HBV CRN North Texas Consortium: Stacey Minshall, R.N., B.S.N. (Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center at Dallas, Dallas, TX), Sheila Bass (University of Texas Southwestern, Dallas, TX). Los Angeles Hepatitis B Consortium: Samuel French, M.D., Velma Peacock, R.N. (David Geffen School of Med, UCLA, Los Angeles, CA). San Francisco Hepatitis B Research Group Consortium: Ashley Ungermann, M.S., Claudia Ayala, M.S., Emma Olson, B.S., Ivy Lau, B.S. (University of California-San Francisco, San Francisco, CA), Veronika Podolskaya, B.S., N.C.P.T., Nata DeVole, R.N. (California Pacific Medical Center, Research Institute). Michigan Hawaii Consortium: Barbara McKenna, M.D., Kelly Oberhelman, P.A.C., Sravanthi Kaza, B.pharm., Cassandra Rodd, B.S. (University of Michigan, Ann Arbor, MI), Leslie Huddleston, N.P., Peter Poerzgen, Ph.D. (The Queen's Medical Center, Honolulu, HI). Chapel Hill, NC Consortium: Jama M. Darling, M.D., A. Sidney Barritt, M.D., Tiffany Marsh, B.A., Vikki Metheny, A.N.P., Danielle Cardona, P.A.-C. (University of North Carolina at Chapel Hill, Chapel Hill, NC). Virginia Commonwealth University Medical Center: Velimir A. Luketic, M.D., Paula G. Smith, R.N., B.S.N., Charlotte Hofmann, R.N. (Virginia Commonwealth University Health System, Richmond, VA). PNW/Alaska Clinical Center Consortium: Terri Mathisen, R.N., B.S.N., Susan Strom, M.P.H. (University of Washington Medical Center, Seattle WA) Jody Mooney, Lupita Cardona-Gonzalez (Virginia Mason Medical Center, Seattle WA). Liver Diseases Branch, N.I.D.D.K., N.I.H.: Nancy Fryzek, R.N., B.S.N., Elenita Rivera, B.S.N., Nevitt Morris, Vanessa Haynes-Williams. Immunology Center: Mary E. Valiga, R.N., Keith Torrey, B.S., Danielle Levine, B.S., James Keith, B.S., Michael Betts, Ph.D. (University of Pennsylvania, Philadelphia, P.A.), Luis J. Montaner, D.V.M, D.Phil. (Wistar Institute, Philadelphia, PA). Data Coordinating Center: Michelle Danielson, Ph.D., Tamara Haller, Geoffrey Johnson, M.S., Stephanie Kelley, M.S., Sharon Lawlor, M.B.A, Joan M. MacGregor, M.S., Andrew Pelesko, B.S., Donna Stoliker, Ella Zadorozny, M.S. (Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA).

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