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

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List of Abbreviations:

HBV - Hepatitis B virus; IFG- impaired fasting glucose; BMI- body mass index; ALT- alanine aminotransferase; AST- aspartate aminotransferase; OR- odds ratio; HCC- hepatocellular carcinoma; NAFLD- non-alcoholic fatty liver disease; US- United States; HBRN- Hepatitis B Research Network; HBsAg- hepatitis B surface antigen; HIV- human immunodeficiency virus; HDL- high density lipoprotein; HBeAg- hepatitis B e antigen; APRI- AST to platelet ratio index

Keywords: glucose abnormalities, liver inflammation, chronic hepatitis B, migration, Asian

Abstract:

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 multi-ethnic 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 BMI 24.3 Kg/m^2. In this cohort, 26.0% were HBeAg-positive, 43.9% had HBV DNA ≥20,000 IU/mL, and 26.7% ALT ≥2xULN (≥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 US/Canada or foreign-born with migration >20 years ago (25.5%). Obesity (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. ~~Diabetes and prediabetes are~~is prevalent in North American adults with chronic HBV and ~~are~~ is associated with known metabolic risk factors and ALT but not HBV DNA. 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.

Introduction

An estimated 1.25 million individuals in the United States (US) 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 US 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 the 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, 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 non-diabetics 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 viral and metabolic effect may accelerate the 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 pre-diabetes and intervention with lifestyle modification and/or pharmacologic therapy is currently recommended (14). IFG is exceedingly prevalent in North America, affecting about 37% of adults aged 20 years and older (15). The limited information to date, predominantly from HBV endemic regions, shows that the prevalence of diabetes among persons with chronic HBV infection varies among countries and ranges from 6-14% (16-19). In a study

using data from the National Health and Nutrition Examination Survey III where only about 0.4% of the 15,866 subjects had chronic hepatitis B, prevalence of diabetes was reported as 7.0 ± 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). These studies however may not be applicable to the North American HBV-infected population due 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.

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 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 HIV coinfection, and who were not receiving antiviral therapy. For this study, participants with acute HBV infection, who were pregnant, and did not have known baseline diabetes status or fasting glucose values within 6 months of the baseline visit were excluded. American Diabetes Association recommends diagnosis of diabetes or prediabetes based on hemoglobin A1C or plasma glucose - fasting levels or 2-h 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 anti-diabetic

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medications or fasting glucose ≥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 (IRB) (Research Ethics Board [REB] 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 ± standard deviation (SD) as appropriate. Overweight was defined as 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 ≥88 cm for women (≥80 for Asian women) and ≥102 cm for men (≥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. 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) × 100 (27). Alcohol consumption was graded as none or minimal (<1 drink per month), moderate (≤4 drinks/day or 14/week in men, ≤3 drinks/day or 7/week in women) or heavy (not moderate) (28).

The non-parametric 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 numeric value of 1 represented the records with missing values (29). Through this technique, all records were kept in the regression models. SAS version 9.3 was used for all analyses.

Results:

Of the total of 1559 consecutive and non-pregnant 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 (Figure 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) (Supplemental 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%), while 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) (Figure 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 US/Canada or foreign born with more than 20 years of migration to US/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) (Figure 3A). Although the overall rate of

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diabetes was higher in HBeAg-negative than in HBeAg-positive patients (13.4% vs 7.8%), when stratified by age, the overall prevalence of glucose abnormalities (IFG versus diabetes versus normal glucose) in HBeAg-positive and HBeAg-negative patients was not different (p=0.47) (Figure 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 (≥2 x ULN) levels were nearly two times more likely to have diabetes compared with those with lower ALT (OR 1.86, 95%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, while 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). Since only 18.7% of patients had a known estimated duration of HBV infection that differed from age (due to assumed non-vertical transmission as the mode of infection), duration of HBV infection was not included in the multivariable models.

Impact of duration of immigration to US or Canada on diabetes prevalence in patients with chronic HBV infection

Being a recent immigrant, defined as having moved to the US 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 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

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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 due 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 as impaired glucose metabolism has been shown to promote liver fibrosis (8-10) and to increase the risk of HCC (4). This study evaluated the prevalence of glucose abnormalities and the associated factors in a large cohort of multi-ethnic HBV-infected persons residing in the US and Canada. We demonstrated that nearly a quarter of this cohort had diabetes (13%) or prediabetes (8%). Current estimates of prevalence of diabetes in US and Canadian adults are 9% and 8%, respectively(15) (31) and approximately 37% of the US 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 US 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 potentially important means of decreasing the risk of liver disease progression in this population.

Prior 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 ER stress (34). Alternatively, the elevated ALT among diabetics may reflect concurrent fatty liver, though liver biopsy or standardized

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imaging data was 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.

While 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 while 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 in 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 American Diabetes Association guidelines for prevention of type 2 diabetes recommends that patients with prediabetes be referred to an intensive diet and physical activity behavioral counselling program targeting loss of 7% body weight and metformin therapy may also be considered especially for those with BMI>35 kg/m^2, aged<60 years, and prior 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 seen 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 US/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 prior studies of Chinese Asian population that also did not show a significant influence of length of migration on

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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. While 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 due 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. As the racial and potentially age distribution of HBRN cohort is different from the general population in US and Canada, it is not possible to directly compare the prevalence of IFG/diabetes to the general population. Due 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 non-invasive 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, while use of oral glucose tolerance test may diagnose more people with diabetes than A1C or fasting glucose cut points (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 US and Canada. Among the foreign-born HBV-infected population, who account for the majority of HBV infections in the US and Canada, we found duration of residence in the US/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, since 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.

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Figure legends:

Figure 1: Schema of patient selection.

Figure 2: The prevalence of normal glucose, IFG, and diabetes among various racial groups.

Figure 3: A. The prevalence of normal glucose, IFG, and diabetes according to baseline ALT: normal, 1-2x

upper limit of normal (ULN), and >2x ULN, stratified by age group (overall p=0.04). **B**. The prevalence of

normal glucose, IFG, and diabetes in HBeAg+ and in HBeAg-negative patients, stratified by age group (overall

p=0.47).

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Table 1: Prevalence of normal glucose levels, IFG, and diabetes among various host and viral patient characteristics

HBV Related Characteristics				
	Normal Glucose Levels	**IFG**	**Diabetes**	**P-value***
ALT level (%)				
≥2 x ULN (n=233)	77.3	6.4	16.3	0.05
<2 x ULN (n=639)	81.1	8.5	10.5	
HBV DNA level (%)				**0.02**
≥20,000 IU/mL (n=380)	83.7	5.3	11.1	
<20,000 IU/mL (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	
Gender (%)				**0.03**

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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**
US/Canada birth (n=144)	70.1	8.3	21.5	
Foreign-born and migrated >20 years (n=268)	76.9	7.5	15.7	
	86.6	7.5	5.9	
Foreign-born and migrated ≤20 years (n=426)	62.8	11.6	25.6	
Foreign-born but unknown migration time (n=43)				
Waist circumference category adjusted for race and gender (%),cm				**0.01**
High risk (n=290)	78.6	8.6	12.8	
Low risk (n=435)	86.7	6.0	7.4	

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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	

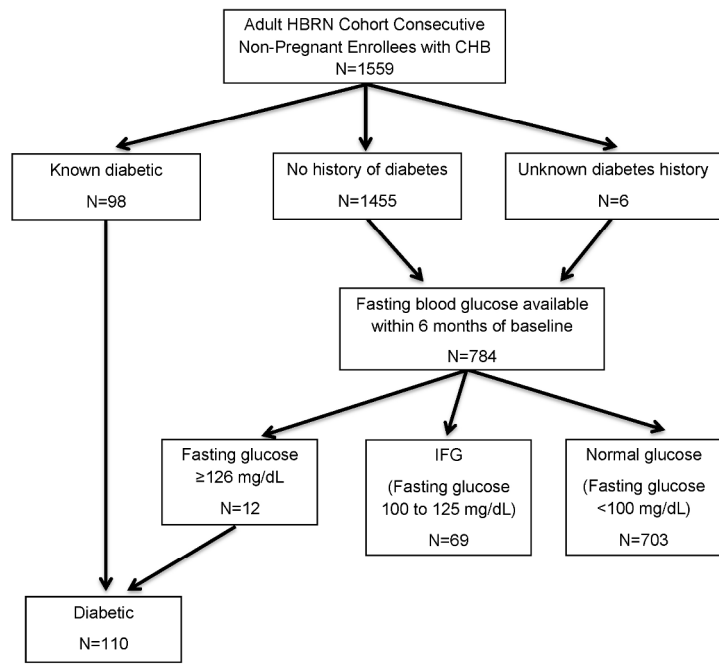*P values are for all group comparison and P <0.05 (2-sided) is considered statistically significant.

Table 2: Factors independently associated with IFG and diabetes among patients with chronic HBV

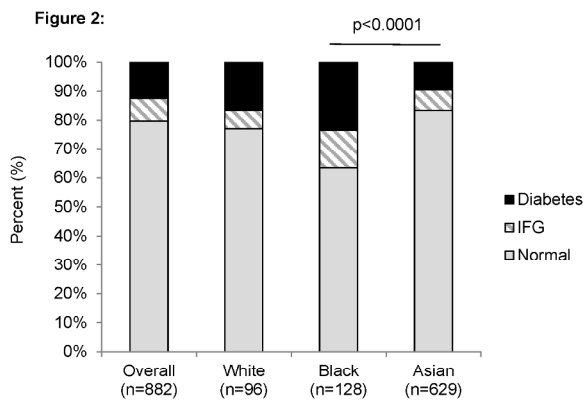| Predictors	IFG		Diabetes	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Age (per decade)	1.23 (0.95, 1.59)	0.11	1.83 (1.41, 2.39)	**<0.0001**
Male gender	1.64 (0.93, 2.90)	0.06	1.43 (0.84, 2.45)	0.19
Race (versus white)				
Black	2.79 (0.97, 8.00)	0.06	1.68 (0.69, 4.10)	0.25
Asian	1.94 (0.74, 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 (versus 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 x ULN)			1.86 (1.05, 3.30)	**0.03**
HBeAg-positive status	0.39 (0.16, 0.98)	**0.044**		

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Table 3: Factors independently associated with diabetes among Asians versus non-Asians with chronic HBV

	Non-Asian N= 229		Asian N=584	
Predictors	**Odds Ratio (95% CI)**	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Age (per decade)	1.71 (1.09, 2.64)	**0.02**	1.87 (1.33, 2.64)	**0.0004**
Male gender	2.02 (0.81, 5.02)	0.13	1.17 (0.58, 2.37)	0.66
Race-adjusted BMI categories (versus 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 (versus US/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 (≥2x ULN)	2.30 (0.82, 6.47)	0.11	1.20 (0.56, 2.57)	0.63

5

Adult HBRN Cohort Consecutive
Non-Pregnant Enrollees with CHB
N=1559

Known diabetic
N=98

No history of diabetes
N=1455

Unknown diabetes history
N=6

Fasting blood glucose available
within 6 months of baseline
N=784

Fasting glucose
≥126 mg/dL
N=12

IFG
(Fasting glucose
100 to 125 mg/dL)
N=69

Normal glucose
(Fasting glucose
<100 mg/dL)
N=703

Diabetic
N=110

215x279mm (300 x 300 DPI)

Figure 2:

p<0.0001

215x279mm (300 x 300 DPI)

Figure 3A:

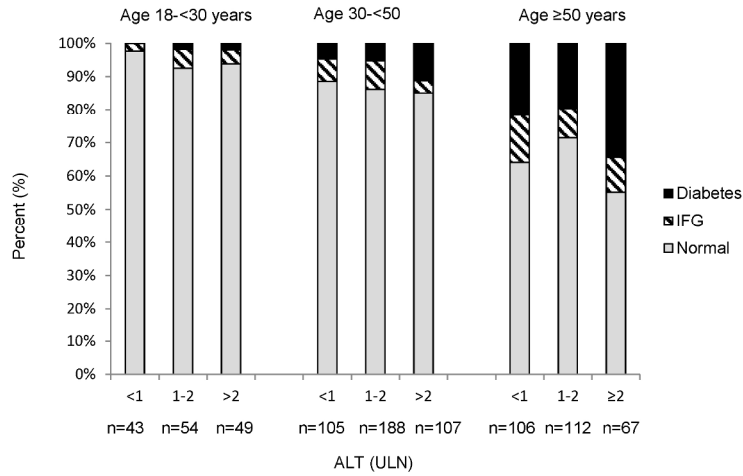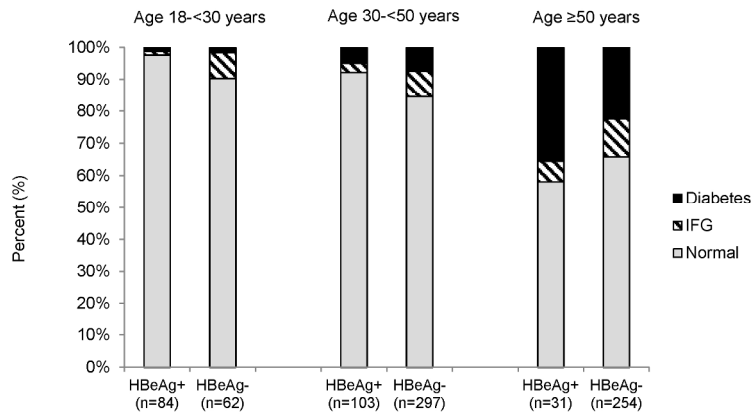**Figure 3B.**

215x279mm (300 x 300 DPI)

Supplemental Table 1: Baseline characteristics of patients with normal glucose levels, IFG, and diabetes.

Characteristic	Normal Glucose Levels (N=703)	IFG (N=69)	Diabetes (N=110)	P-value*
Age, median (range), years	41.3 (18-78)	49.8 (21-75)	54.9 (28-80)	**<0.0001**
Female (%)	49.4	34.8	40.9	**0.03**
Race (%)				**<0.0001**
White	10.5	8.7	14.5	
Black	11.5	24.6	27.3	
Asian	74.5	65.2	54.5	
Other	3.4	1.4	3.6	
Continent of birth (%)				**0.0006**
Africa	9.1	18.8	9.2	
Asia	70.4	62.3	53.2	
Europe	4.3	1.4	2.8	
North America	15.5	17.4	32.1	
South America	0.6	0	1.8	
Australia	0.1	0	0.9	
Birth and migration status (%)				**<0.0001**
US/Canada born	14.4	17.4	28.4	
Foreign-born and migrated >20 years	29.3	29.0	38.5	
Foreign-born and migrated ≤20 years	52.5	46.4	22.9	
Foreign-born but unknown migration time	3.8	7.2	10.1	

Waist circumference, median (range), cm	83.8 (51-198)	87.5 (71-145)	90.2 (66-155)	**<0.0001**
Median BMI (range) Kg/m^2	23.7 (15-45)	26.7 (18-44)	26.8 (18-50)	**<0.0001**
Race-adjusted BMI (%)				**<0.0001**
Normal	44.9	17.9	20.4	
Overweight	40.4	43.3	37.9	
Obese	14.7	38.8	41.7	
Alcohol consumption in the previous 12 months (%)				0.5
None	73.5	73.1	77.3	
Moderate	20.1	20.9	13.6	
Heavy	6.4	6.0	9.1	
Hypertension history (%)	12.0	42.0	65.1	**<0.0001**
Hyperlipidemia history (%)	8.5	20.3	54.5	**<0.0001**
Family history of diabetes (%)	32.3	37.7	66.4	**<0.0001**
Significant fibrosis (by APRI score >1.50) (%)	4.6	1.5	8.2	0.1
High ALT				
≥2 x ULN (%)	25.8	21.7	36.2	0.05
>1 X ULN (%)	69.1	65.2	70.5	0.8
High HBV DNA level (≥20,000 IU/mL) (%)	46.0	29.4	39.6	**0.02**
HBeAg-positive (%)	28.9	9.2	17.0	**0.0002**
Estimated duration of HBV infection,	32 (0-71)	31 (1-61)	38 (1-71)	0.07

median (range), years				

*P values are for all group comparison and P <0.05 (2-sided) is considered statistically significant.