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Prevalence of and Factors Influencing Impaired Glucose Tolerance Among Hepatitis B Carriers

A Nationwide Cross-Sectional Study in the Republic of Korea

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Abstract: Diabetes is associated with a poor prognosis for liver disease, particularly in chronic hepatitis carriers. We investigated the prevalence of factors associated with impaired glucose tolerance (IGT) including diabetes and impaired fasting glucose (IFG) among individuals with hepatitis B virus (HBV) infection.

We used data from the Korean National Health and Nutrition Examination Survey, a nationwide cross-sectional survey conducted between 2007 and 2011. Sociodemographic information was collected using a structured questionnaire. The HBV surface antigen, liver enzymes, and lipid profile were measured from blood samples.

IFG was found in 18.1% of HBV carriers and 19.3% of noncarriers ($P = 0.25$). Diabetes was observed in 10.0% of HBV carriers and 12.2% of noncarriers ($P = 0.08$). Lower level of educational attainment was associated with a higher prevalence of IGT: high school education (odds ratio [OR] = 1.94 [95% confidence interval (CI) 1.14–3.29] and less than a high school education (OR = 3.20 [95% CI, 1.66–6.15] vs more than or equal to a college education. Elevated alanine transaminase and triglyceride by 10 were associated with increased risk of IGT (OR = 1.10 [95% CI, 1.01–1.20] and OR = 1.04 [95% CI, 1.01–1.07], respectively). Being a man and older in age were associated with a higher prevalence of IGT, and individuals with a low body mass index were at lower risk for IGT.

Given the synergistic effect of diabetes and HBV infection on liver disease prognosis, we recommend targeted IGT screening and follow-up for HBV carriers. These efforts should include health policies and intervention programs aimed at reducing educational disparities and encouraging early control of elevated liver enzymes or lipid profiles.

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Abbreviations: ALT = alanine transaminase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, HbA1c = hemoglobin A1c, HBV = hepatitis B virus, HBsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IFG = impaired fasting glucose, KNHANES = Korean National Health and Nutrition Examination Survey, OR = odds ratio, TG = triglyceride.

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INTRODUCTION

The liver has a unique role in controlling carbohydrate metabolism by maintaining glucose level within the normal range.[1] The association between increased insulin resistance and chronic liver disease is well known and beside those associated with lifestyle, which are known to increase the risk of type 2 diabetes, it may contribute to the pathophysiology of glucose intolerance in patients with liver diseases distinctively.[2] In most patients, insulin resistance and glucose intolerance develop in the early stages of chronic liver disease,[3] and the natural history of diabetes caused by liver disease differs from that of type 2 diabetes.[4] Diabetes or insulin resistance in patients with liver disease is associated with a poor prognosis including rapid progression, drug resistance, and poor control of glucose levels.[4,5]

Previous investigations of the relationship between cirrhosis of the liver and the development of impaired glucose tolerance have shown that 60% to 80% of patients with cirrhosis suffer from glucose intolerance and 20% to 60% of those have diabetes.[5] Several previous studies have investigated whether viral infections of liver promote insulin resistance and cause impaired glucose metabolism, and most have focused on the hepatitis C viruses (HCVs) and hepatitis B viruses (HBVs) because of their chronicity.[6] Although the association between HCV infection and the development of impaired glucose tolerance because of insulin resistance is widely acknowledged,[6,7] the relationship between impaired glucose tolerance and HBV infection is controversial.[6,8]

Diabetes itself is a well-known independent risk factor for liver cirrhosis and hepatocellular carcinoma (HCC)[9,10] and aggravates the condition.[5] Diabetes increases the risk of liver cirrhosis[11] and HCC[5,12] in patients with an HBV or HCV infection, and recent reports have suggested that diabetes and hepatitis infection have a synergistic effect on the risk of developing HCC.[13,14] Thus, patients with both HBV or HCV infection and impaired glucose tolerance are at high risk for advanced liver diseases such as cirrhosis and HCC.

HBV and HCV infections are major global public health issues with >2 billion HBV-infected individuals, 378 million chronic HBV carriers, and 130 million HCV-infected people worldwide.[15,16] However, the regional distribution of HBV and HCV infection varies. HCV is more prevalent in

Western countries, whereas HBV is endemic to the Asia-Pacific region where 75% of chronic HBV carriers reside and 15% to 25% die of HBV-related liver diseases.[17] The Republic of Korea had a high prevalence of HBV infection in the 1980s,[18] and although the prevalence decreased following implementation of the nationwide vaccination program in 1995, the Republic of Korea remains one of the highest HBV-endemic areas in the Asia-Pacific region.[19]

Given the high prevalence of HBV infection in the Republic of Korea and its potential association with diabetes, it is important to determine whether the prevalence of diabetes is higher among people infected with HBV than among those who are HBV negative. Thus, we compared the prevalence of diabetes and impaired fasting glucose (IFG) and diabetes management in HBV carriers with those in noncarriers. Moreover, we used a nationally representative sample of the Republic of Korea population to identify possible predictors of impaired glucose tolerance including IFG and diabetes, the major factors that act synergistically with HBV to cause liver disease progression in HBV carriers.

METHODS

Study Population

We used data from the Korean National Health and Nutrition Examination Survey (KNHANES) conducted between 2007 and 2011. The KNHANES is a population-based cross-sectional survey of a nationally representative sample in the Republic of Korea. The KNHANES was conducted every 3 years between 1998 and 2005 and has been conducted yearly since 2007 using an independent rolling survey sampling model. Trained interviewers used a standardized questionnaire to assess health-related behaviors, the medical examination was conducted by well-trained nurses and physicians, and a food-frequency questionnaire was used to assess dietary intake. The official KNHANES website describes the study in detail (http://knhanes.cdc.go.kr/). The study protocol was approved by the institutional review board of the Korea Centers for Disease Control and Prevention (IRB no. 2011-02CON-06-C) and the institutional review board of the National Cancer Center (IRB no. NCCNCS-08-129), and all participants provided written informed consent.

Among the 53,232 individuals sampled between 2007 and 2011, 42,347 agreed to participate in the survey (total response rate, 79.6%). Participants who were 30 years of age or older were included in the study. Individuals whose serum hepatitis B surface antigen (HBsAg) was positive were defined as HBV carriers and those whose serum HBsAg was negative were defined as HBV noncarriers. The data of people whose serum glucose level was not measured or whose fasting time was <8 hours were excluded from the study. A final total of 23,355 noncarriers and 916 carriers were included in the analysis (Figure 1).

Data Collection

Serum HBsAg, aspartate aminotransferase (AST), and alanine transaminase (ALT) were measured using electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland). Fasting plasma glucose levels, triglycerides (TGs), and total cholesterol were measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). We defined impaired glucose tolerance as fasting glucose $\geq$100 mg/dL or a hemoglobin A1c (HbA1c) level $\geq$6.5%, which included the criteria for IFG (fasting plasma glucose, 100–125 mg/dL) and diabetes (fasting plasma glucose, $\geq$126 mg/dL or HbA1c $\geq$ 6.5%).

The health interview questionnaire comprised demographic and socioeconomic characteristics of the participants including sex, age, area of residence, monthly household income, educational attainment, previous and current diseases, subjective health status, smoking, drinking, and stress level. HBV carriers who reported they had been diagnosed with HBV infection by a physician were classified as being aware of their HBV infection status. Household income was categorized according to interquartile range. Height and weight measured during the medical examination was used to calculate the body mass index (BMI) by dividing weight by height squared (kg/m^2), which was divided into 3 groups: <18.5 kg/m^2, 18.5 to 24.9 kg/m^2, and $\geq$25 kg/m^2. Smoking status was classified as current smokers and noncurrent smokers. Alcohol consumption was classified as heavy drinking and nonheavy drinking based on the results of previous studies showing that low-to-moderate alcohol consumption prevented the development of diabetes.[20,21] Heavy drinking was defined as consuming alcohol twice or more often

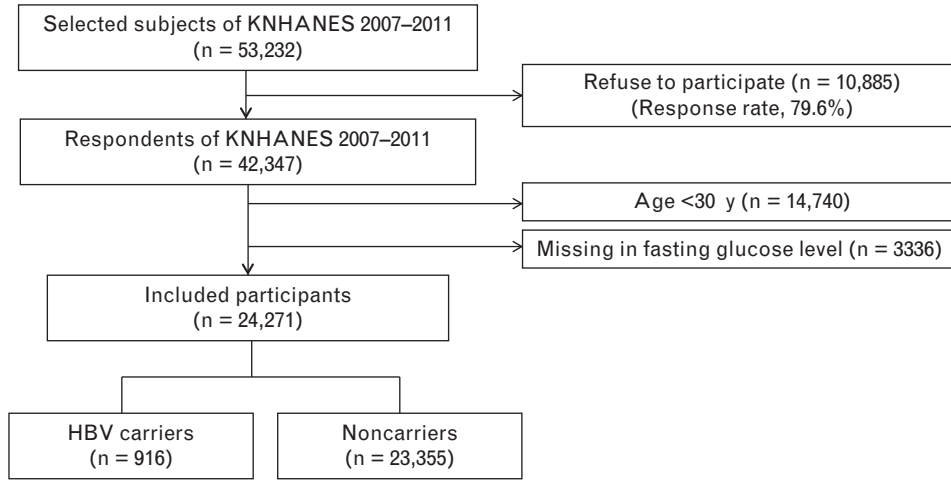

FIGURE 1. Flowchart of the study population. HBV = hepatitis B virus, KNHANES = Korean National Health and Nutrition Examination Surveys.

per week and consuming at least 7 drinks (for men) and 5 drinks (for women) on any given occasion.

Statistical Analyses

Survey sample weights, calculated taking the sampling rate, response rate, and age/sex stratification into consideration, were used in all analyses. The prevalence of IFG and diabetes among HBV carriers and noncarriers was compared using the χ^2 test. In addition, HBV carriers and noncarriers with diabetes were compared according to the prevalence of diabetes recognition, defined as participants who had been diagnosed with diabetes by a physician; diabetes treatment, defined as participants who were prescribed insulin or oral antidiabetic agents; and diabetes control, defined maintaining an HbA1c level <6.5%.

Baseline characteristics of HBV carriers are expressed as percent and 95% confidence intervals (CIs). AST, ALT, TG, and total cholesterol levels are expressed as means (95% CIs). A univariate logistic regression analysis was used to identify factors associated with impaired glucose tolerance and the results were reported as odds ratios (ORs) and 95% CIs. We conducted a multiple logistic regression analysis to assess the independent effect of the variables with a P value <0.20 in the univariate logistic regression to avoid overadjustment by including an excessive number of variables. Missing information was treated as dummy. All statistical analyses were conducted using SAS software version 9.1 (SAS, Inc, Cary, NC).

RESULTS

Figure 2 shows the prevalence of IFG and diabetes in HBV carriers and noncarriers. We found no significant between-group differences in IFG (HBV carriers, 18.1% vs noncarriers, 19.3%; $P = 0.25$) or diabetes (HBV carriers, 10.0% vs noncarriers, 12.2%; $P = 0.08$). Moreover, the prevalence of diabetes recognition, treatment, and control was not significantly different between the HBV carriers and noncarriers ($P = 0.66$, 0.54, and 0.43, respectively).

Table 1 shows the characteristics of HBV carriers in the Republic of Korea. A total of 52.2% were men and 47.8% were women, and 60.8% had a normal BMI defined as 18.5 to 24.9 kg/m^2. Most HBV carriers (78.9%) were not aware of their infection status: nearly 50% rated their health status as moderate, 43.8% were smokers, and 11.5% were heavy drinkers. The mean AST, ALT, TG, and total cholesterol were 28.8 IU/L (95% CI, 27.2–30.3), 29.9 IU/L (95% CI, 27.2–32.6), 116.5 mg/dL (95% CI, 111.1–121.9), and 184.6 mg/dL (95% CI, 182.0–187.2), respectively.

Table 2 shows the factors associated with impaired glucose tolerance in HBV carriers. Being a man, older in age, lower household income, lower educational attainment, smoking, and increments in AST, ALT, and TG levels were significantly associated with a higher risk of impaired glucose tolerance ($P < 0.05$), whereas lower BMI was significantly associated with lower risk of impaired glucose tolerance.

Of the variables tested in the univariate analysis, sex, age, household income, educational attainment, BMI, smoking, AST, ALT, and TG levels that reached $P < 0.20$ were included in the multivariate analysis (Table 3). Being a man was significantly associated with a higher prevalence of impaired glucose tolerance (OR = 2.18 [95% CI, 1.28–3.72]). Old age was associated with impaired glucose tolerance: 40 to 49 years, OR = 2.34 (95% CI, 1.25–4.41); 50 to 59 years, OR = 2.31 (95% CI, 1.14–4.67); and ≥60, OR = 3.28 (95% CI, 1.61–6.71) vs <40 years of age. Lower educational attainment was related to a higher prevalence of impaired glucose tolerance: high school education, OR = 1.94 (95% CI, 1.14–3.29) and less than a high school education, OR = 3.20 (95% CI, 1.66–6.15) vs more than or equal to a college education. People with lower BMI had a lower risk for impaired glucose tolerance: BMI 18.5 to 24.9 kg/m^2, OR = 0.42 (95% CI, 0.29–0.61) and BMI <18.5 kg/m^2, OR = 0.25 (95% CI, 0.05–1.24) compared with overweight participants. Increments of 10 in ALT and TG level increased the risk of impaired glucose tolerance (ALT, OR = 1.10 [95% CI, 1.01–1.20]; and TG, OR = 1.04 [95% CI, 1.01–1.07], respectively).

DISCUSSION

We found that 18.1% of HBV carriers in the Republic of Korea had IFG and 10.0% had diabetes. Furthermore, the percentages of IFG and diabetes were similar in noncarriers. Our results support several previous studies showing that in the absence of cirrhosis, the prevalence of diabetes among HBV

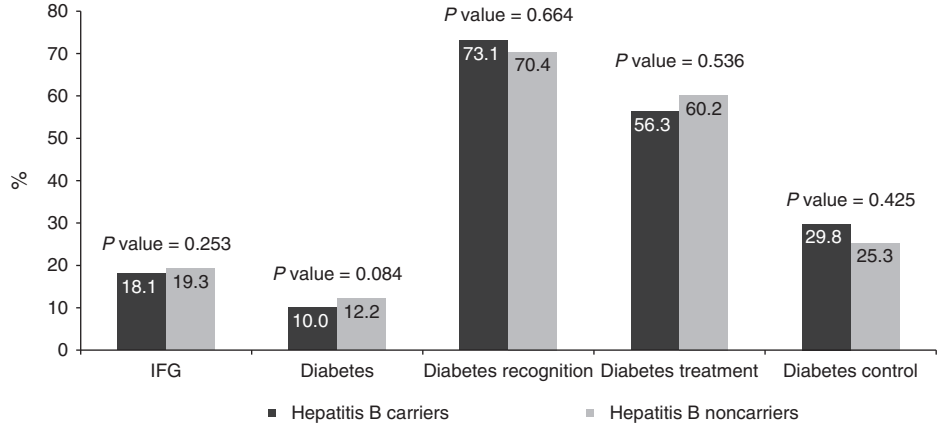

FIGURE 2. Prevalence of IFG, diabetes, diabetes recognition, treatment, and control in HBV carriers and noncarriers. IFG: fasting plasma glucose 100 to 125 mg/dL. Diabetes: fasting plasma glucose ≥126 mg/dL or HbA1c ≥ 6.5%. Diabetes recognition: participants who had been diagnosed with diabetes by a physician. Diabetes treatment: participants with diabetes who were prescribed insulin or oral antidiabetic agents. Diabetes control: participants with diabetes who maintained an HbA1c level <6.5%. HbA1c = hemoglobin A1c, HBV = hepatitis B virus, IFG = impaired fasting glucose.

TABLE 1. Weighted Prevalence of Baseline Characteristics for HBV Carriers

	N	Prevalence, %	95% CI
Fasting glucose level			
Normal (<100 mg/dL)	655	72.0	(68.5–75.4)
IFG (100–125 mg/dL)	171	18.1	(15.3–20.9)
Diabetes (≥126 mg/dL or HbA1c ≥ 6.5%)	90	10.0	(7.5–12.4)
Sex			
Men	442	52.2	(48.4–56.0)
Women	474	47.8	(44.0–51.6)
Age, y			
30–39	224	25.5	(22.1–29.0)
40–49	238	27.0	(23.4–30.6)
50–59	214	23.7	(20.3–27.2)
≥60	240	23.7	(20.5–27.0)
Area of residence			
Urban	680	78.8	(74.7–82.8)
Rural	236	21.2	(17.2–25.3)
Household income			
Low	158	15.3	(12.6–18.0)
Mid-low	232	26.1	(22.6–29.6)
Mid-high	228	26.3	(22.8–29.8)
High	278	30.3	(26.8–33.8)
Missing	20	1.9	(0.9–2.9)
Education			
<High school	358	35.6	(31.7–39.4)
High school	290	31.9	(28.2–35.7)
≥College	258	30.4	(26.4–34.5)
Missing	10	2.1	(0.8–3.4)
BMI, kg/m^2			
<18.5	24	2.9	(1.6–4.2)
18.5–24.9	565	60.8	(57.1–64.4)
≥25.0	324	35.9	(32.3–39.4)
Missing	3	0.5	(0.0–1.1)
Awareness of HBV infection			
Unaware	723	78.9	(75.6–82.1)
Aware	193	21.1	(17.9–24.4)
Subjective health status			
Poor	227	21.2	(18.2–24.3)
Moderate	420	50.2	(46.3–54.2)
Good	259	26.5	(23.0–29.9)
Missing	10	2.1	(0.8–3.4)
Stress level			
High	242	24.0	(20.8–27.2)
Low	666	74.3	(71.1–77.5)
Missing	8	1.7	(0.5–2.8)
Smoking status			
Current smoker	372	43.8	(39.9–47.7)
Noncurrent smoker	535	54.5	(50.6–58.3)
Missing	9	1.8	(0.6–2.9)
Alcohol drinking			
Heavy drinker	93	11.5	(9.0–14.0)
Nonheavy drinker	812	86.5	(83.9–89.1)
Missing	11	2.0	(0.8–3.3)
AST			
Mean, IU/L	916	28.8	(27.2–30.3)
ALT			
Mean, IU/L	916	29.9	(27.2–32.6)
TGs			
Mean, mg/dL	916	116.5	(111.1–121.9)
Total cholesterol			
Mean, mg/dL	916	184.6	(182.0–187.2)

ALT = alanine transaminase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, HbA1c = hemoglobin A1c, HBV = hepatitis B virus, IFG = impaired fasting glucose, TG = triglyceride.

carriers does not differ from that of the general population.[11,22] A study that compared the risk for diabetes in patients with asymptomatic chronic HBV infection and noncarriers found no statistically significant difference between the groups.[23] These results, together with the finding that impaired glucose tolerance risk is increased in advanced liver diseases caused by HBV infections such as cirrhosis,[4] suggest that HBV-related parenchymal damage, rather than HBV infection itself, causes impaired glucose tolerance.[23] Although previous studies have found a higher prevalence of diabetes in chronic HBV carriers than in noncarriers,[8,24] we could not readily compare those results with ours given the heterogeneous population characteristics between the studies such as the stage of liver disease. Maintaining good control of diabetes is difficult in patients with liver disease because pharmacological therapies are limited by hepatotoxicity and the risk of hypoglycemia.[5,25] However, we found that the proportions of HBV carriers with diabetes undergoing diabetes treatment (as defined by the prescription of insulin or oral antidiabetic agents) or meeting the criteria for well-controlled diabetes (HbA1c < 6.5%) were not significantly different from those of noncarriers with diabetes. Furthermore, the proportion of HBV carriers with controlled diabetes in our study (29.8%) was similar to that of a previous study (28.7%).[25]

The facts that the HBV infection had been diagnosed by a physician in only 21.1% of the HBV carriers and 76.7% of respondents reported their subjective health status as moderate or good (Table 1) suggest that most of the HBV carriers in our study were asymptomatic. In addition, only 1.9% (18/916, data not shown) of our HBV carriers had been diagnosed with cirrhosis of the liver. Thus, we concluded that, in our sample, the prevalence rate of IFG and diabetes and the status of diabetes management did not differ between HBV carriers and noncarriers.

Among the factors associated with impaired glucose tolerance in HBV carriers, male sex, older age, lower level of educational attainment, higher BMI, and increments in ALT and TG levels were independently associated with impaired glucose tolerance (IFG or diabetes). We believe that the educational disparity in prevalence of impaired glucose tolerance in HBV carriers is of particular importance. Although previous studies have shown an association between lower educational attainment and a higher prevalence of diabetes in the general population, and its widening disparity,[26,27] the association between education level and impaired glucose tolerance was stronger in our study, which focused on HBV carriers. The OR was >3 for HBV carriers who had less than a high school education compared with carriers who had a college education, indicating that the educational disparity was greater among HBV carriers than the general population. In the Republic of Korea, graded differences in mortality resulting from liver cancer and liver diseases have been observed in both sexes, showing higher mortality rates associated with lower educational level, and these differences are more obvious in the younger population, reflecting significant inequalities.[28] Our finding of an association between educational level and the prevalence of impaired glucose tolerance, which is associated with poor HBV infection prognosis[4,5] among HBV carriers, may partially explain the educational disparities in mortality resulting from liver cancer and liver diseases in the Republic of Korea.

A second important finding of our study was that an increment in ALT and TG levels was independently associated with impaired glucose tolerance. ALT is a specific marker for hepatocellular injury and changes in the lipid profile may serve

TABLE 2. Weighted Univariate Logistic Regression Analysis of Factors Associated With IFG and Diabetes in HBV Carriers

	IFG and DM	Normal			
	N, %	N, %	OR	95% CI	*P* Value
Sex					
Men	147 (60.6)	295 (49.0)	1.60	(1.13–2.26)	0.01
Women	114 (39.4)	360 (51.0)	1		
Age, y					
30–39	26 (10.6)	198 (31.4)	1		
40–49	62 (26.6)	176 (27.2)	2.89	(1.60–5.22)	<0.001
50–59	71 (27.0)	143 (22.5)	3.55	(1.96–6.41)	<0.001
≥60	102 (35.8)	138 (19.0)	5.57	(3.17–9.80)	<0.001
Area of residence					
Urban	195 (80.3)	485 (78.1)	1.14	(0.77–1.70)	0.51
Rural	66 (19.7)	170 (21.9)	1		
Household income					
Low	61 (23.9)	97 (12.5)	2.35	(1.37–4.02)	0.002
Mid-low	70 (28.5)	162 (25.9)	1.34	(0.84–2.16)	0.22
Mid-high	55 (21.0)	173 (29.1)	0.88	(0.54–1.43)	0.60
High	68 (26.6)	210 (32.5)	1		
Education					
<High school	141 (53.1)	217 (29.8)	3.52	(2.25–5.50)	<0.001
High school	66 (28.6)	224 (34.2)	1.65	(1.07–2.54)	0.02
≥College	52 (18.3)	208 (36.0)	1		
BMI, kg/m^2					
<18.5	2 (1.1)	22 (3.6)	0.17	(0.04–0.77)	0.02
18.5–24.9	126 (46.4)	439 (66.8)	0.39	(0.28–0.55)	<0.001
≥25.0	132 (52.5)	192 (29.6)	1		
Awareness of HBV infection					
Unaware	213 (80.3)	510 (78.3)	1.13	(0.74–1.72)	0.59
Aware	48 (19.7)	145 (21.7)	1		
Subjective health status					
Poor	78 (26.5)	149 (19.8)	1.28	(0.81–2.03)	0.29
Moderate	111 (45.5)	309 (53.5)	0.81	(0.54–1.22)	0.32
Good	68 (28.0)	191 (26.7)	1		
Stress level					
High	66 (23.2)	176 (24.9)	0.91	(0.62–1.35)	0.64
Low	192 (76.8)	474 (75.1)	1		
Smoking status					
Current smoker	122 (52.0)	250 (41.7)	1.51	(1.09–2.11)	0.02
Noncurrent smoker	135 (48.0)	400 (58.3)	1		
Alcohol drinking					
Heavy drinker	32 (14.5)	61 (10.7)	1.41	(0.84–2.38)	0.26
Nonheavy drinker	225 (85.5)	587 (89.3)	1		
AST					
10% increments, mean (SE)	32.1 (1.6)	27.5 (0.9)	1.10	(1.02–1.18)	0.02
ALT					
10% increments, mean (SE)	37.0 (4.2)	27.1 (1.1)	1.07	(1.01–1.13)	0.01
TGs					
10% increments, mean (SE)	136.4 (5.6)	108.7 (3.2)	1.05	(1.02–1.08)	<0.001
Total cholesterol					
10% increments, mean (SE)	186.8 (2.2)	183.7 (1.6)	1.02	(0.98–1.07)	0.32

ALT = alanine transaminase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, DM = diabetes, HBV = hepatitis B virus, IFG = impaired fasting glucose, OR = odds ratio, SE = standard error, TG = triglyceride.

as a marker for the severity of liver injury.[29] Moreover, increased serum lipid resulting from abnormal fat metabolism contributes to impaired glucose tolerance by causing hepatic TG accumulation.[30] Several previous studies have shown that high levels of liver enzymes such as ALT, or dyslipidemia are related to IFG or diabetes in HBV/HCV carriers.[31–33] Our results indicate that elevated ALT or TG levels even below the threshold of abnormality can increase the risk for impaired glucose tolerance. Thus, close monitoring of liver enzymes and lipid profile to enable early control of elevated ALT and TG levels may be crucial for the prevention of impaired glucose tolerance in HBV carriers.

TABLE 3. Weighted Multivariate Logistic Regression† Analysis of Factors Associated With IFG and Diabetes in HBV Carriers

	OR	95% CI
Sex		
Men	2.18	(1.28–3.72)*
Women	1	
Age, y		
<40	1	
40–49	2.34	(1.25–4.41)*
50–59	2.31	(1.14–4.67)**
≥60	3.28	(1.61–6.71)*
Household income		
Low	1.26	(0.66–2.40)
Mid-low	0.87	(0.51–1.51)
Mid-high	0.90	(0.52–1.55)
High	1	
Education		
<High school	3.20	(1.66–6.15)*
High school	1.94	(1.14–3.29)**
≥College	1	
BMI, kg/m^2		
<18.5	0.25	(0.05–1.24)
18.5–24.9	0.42	(0.29–0.61)**
≥25.0	1	
Smoking status		
Current smoker	0.93	(0.56–1.55)
Noncurrent smoker	1	
AST		
10 increments	0.97	(0.86–1.09)
ALT		
10 increments	1.10	(1.01–1.20)**
TGs		
10 increments	1.04	(1.01–1.07)**

ALT = alanine transaminase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, HBV = hepatitis B virus, IFG = impaired fasting glucose, OR = odds ratio, TG = triglyceride.

*$P < 0.01$.

**$P < 0.05$.

†P values <0.20 in the univariate analysis were included.

Other factors that were significantly associated with impaired glucose tolerance in our study, including male sex, older age, and being overweight, are well-known risk factors for the development of diabetes in the general population[34,35] and in viral hepatitis carriers.[23,31,36,37]

Our study had several limitations. First, we measured only HBsAg and hepatitis B surface antibodies because total hepatitis B core antibodies were not included in the KNHANES protocol. Thus, we were only able to assess current HBV infections. Second, a previous study found a strong association between IFG and the hepatitis B e-antigen, a marker for HBV replication and infectivity,[31] and an increase in γ-glutamyl transferase, which may reflect hepatic oxidative stress.[31–33] We were unable to compare our results with theirs because data were lacking in our study. Third, our cross-sectional study design did not allow us to assess the causal order of the association (temporal relationship) among HBV infection, sociodemographic, and laboratory factors and the development of impaired glucose tolerance. Fourth, the information collected from the health interview was self-reported and may have been subject to information or recall bias. However, a major strength of our study is that the data were obtained from a nationally representative survey, and we applied sampling weights in the analysis to represent the entire Korean population. Thus, the results are representative and may be generalized to all HBV carriers in Asian countries whose HBV epidemiology is similar to that of Korea. Moreover, to the best of our knowledge, the present study is the first to investigate the prevalence of impaired glucose tolerance, diabetes management, and associated sociodemographic factors in HBV carriers.

The burden of liver disease related to HBV infection is substantial.[18,19] In the Republic of Korea, mortality related to liver cancer and liver disease is considerable;[28] liver cancer is the fifth most commonly diagnosed cancer and the second leading cause of cancer-related death.[38] Given that diabetes is associated with a poor prognosis for liver disease and the development of liver cirrhosis[11] and HCC[5,12] in HBV carriers, it is imperative that factors associated with the development of diabetes are well managed in people with an HBV infection to prevent the development of end-stage liver disease. Both IFG (plasma glucose, 100–125 mg/dL) and diabetes (plasma glucose, ≥126 mg/dL or HbA1c ≥ 6.5%) should be monitored in HBV carriers because the natural history of diabetes is a spectrum involving IFG in the early stage. We found that the following factors were associated with impaired glucose tolerance: being a man, older age, lower educational attainment, higher BMI, and increasing increments of ALT and TG levels. Of these factors, it is most important to focus on those that can be modified to decrease the risk of impaired glucose tolerance, such as education and weight control, because of their high impact and association with high mortality resulting from liver disease. HBV carriers with impaired glucose tolerance are at high risk for end-stage liver disease, and therefore HBV carriers should be considered for surveillance programs that closely monitor liver enzymes and lipid profile and detect changes in ALT and TG levels, so that elevations can be rapidly controlled to prevent impaired glucose tolerance in HBV carriers at an early stage.

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