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Association between self-monitoring of blood glucose and hepatitis B virus infection among people with diabetes mellitus: a cross-sectional study in Gansu Province, China

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ABSTRACT

Objective The purpose was to explore the association between self-monitoring of blood glucose (SMBG) and hepatitis B virus (HBV) infection among people with diabetes.

Design A cross-sectional comparative study.

Setting Six township hospitals in Gansu Province, China in October 2018.

Participants 408 patients with diabetes were systematically recruited, and based on their characteristics 408 people without diabetes were randomly matched 1:1.

Interventions Venous blood was collected for HBV serological testing and blood glucose testing.

Primary and secondary outcome measures The primary outcome was comparison of hepatitis B surface antigen (HBsAg) positive rates between the two groups. The secondary outcome was the relationship between frequency of SMBG and HBsAg positivity.

Results HBsAg positive rate in people without diabetes was 2.0% and in those with diabetes was 4.2%. Whether in people without diabetes or patients with diabetes, higher frequency of SMBG was associated with higher HBsAg positive rate. Increases in the duration of diabetes were correlated with increasing rates of HBsAg. Compared with people without diabetes, logistic regression identified an association between diabetes and HBV infection (OR=2.8; 95% CI 1.0 to 7.6), but impaired fasting glucose was not (OR=2.3; 95% CI 0.5 to 9.9).

Conclusion Routine blood glucose monitoring at home was associated with HBV infection, which meant people with diabetes may be at high risk of HBV infection. China is a country with high prevalence of both HBsAg and diabetes, and the increased risk of HBV infection in populations with diabetes needs more attention.

Strengths and limitations of this study

- ► A population-based, cross-sectional study can identify hepatitis B virus (HBV) infection among populations with diabetes in China.
- ► A 1:1 matching study can reduce the confounding effects of age, gender and other factors.
- ► Stratified analysis is more likely to identify the relationship between diabetes prevalence, frequency of blood glucose monitoring and HBV infection.
- ► This is a study on correlation and causality cannot be inferred.
- ► Questionnaire survey may cause recall bias.

INTRODUCTION

In 2015, an estimated 257 million people in the world were living with hepatitis B virus (HBV) infection.[1] Of the adult population in the Western Pacific Region, 6.2% are infected, which is the highest rate among the WHO regions.[1] Based on the results of a 2006 national serological survey, the adjusted prevalence of hepatitis B surface antigen (HBsAg) in Chinese people 1–59 years of age was 7.2%.[2] According to a model study of global HBV prevalence in 2016, there were 86 million people in China who were HBsAg-positive and the estimated rate of HBsAg prevalence was 6.1%.[3]

China not only has the most carriers of HBsAg, but also the most number of patients with diabetes in the world. The estimated prevalence of total diabetes and prediabetes was 12.8% and 35.2%, respectively, among the Chinese population aged 18 and older between 2015 and 2017.[4] Routine self-monitoring of blood glucose (SMBG) is recommended for diabetes management and therapy by many international and regional guidelines and is considered an important aspect of management of glycaemic control.[5] In China, 19.5% of patients with diabetes reported that they monitored their blood glucose more than once a week,[6] which meant that the absolute number of SMBG was very huge.

Studies in the USA reported a high risk of acute HBV infection in patients with diabetes, and a few articles also showed a higher prevalence of HBsAg in patients with diabetes.[7–12] Two cohort studies using HBV infection as an exposure factor showed that HBV infection has no effect on diabetes development.[13 14] Some studies of people with diabetes have shown that HBV infection, especially acute HBV infection, was probably transmitted during blood glucose monitoring.[15 16]

Currently, there is no sufficient evidence to show an association between SMBG and HBV infection in China. Based on the high prevalences of both HBsAg and diabetes, a hypothesis established in this study was that SMBG may be an important part of HBV infection in patients with diabetes. We investigated the status of HBV infection in people with and without diabetes in China in order to explore the association between SMBG at home and HBV infection, which could provide scientific evidence on the relationship between diabetes and HBV infection.

METHODS

Study population and setting

A comparative cross-sectional study was conducted in Jingyuan County, Gansu Province in October 2018. The setting of this study was selected by convenient sampling. Jingyuan County has a population of approximately 455 000 people living in 18 towns, and 6791 patients with diabetes were recorded by 18 township hospitals. In this study, patients with diabetes who were recorded by the hospital and on treatment were systematically recruited from the six township hospitals with the largest number of patients with diabetes. Participants with diabetes were eligible for the study if they (1) were no less than 18 years old; (2) were diagnosed with diabetes with medical records; and (3) provided informed consent. People without diabetes were randomly recruited from the same township hospitals and were eligible for the study if they (1) were no less than 18 years old; (2) had two or more fasting blood glucose tests that were <7 mmol/L; and (3) provided informed consent. In addition, people without diabetes were matched one to one based on the characteristics of the population with diabetes and were included if they met at least four of the following five conditions: (1) the same sex as the patient with diabetes; (2) the age difference with the patient with diabetes was ≤5 years; (3) the same level of education as the patient with diabetes; (4) the same marital status as the patient with diabetes; and (5) the same occupation as the patient with diabetes. Participants were excluded if they were pregnant at the time of the study, had psychological problems or physical disabilities, and were unable to complete the questionnaire.

We used PASS (Power Analysis and Sample Size, V.15.0.5; NCSS Statistical Software, USA) to calculate the necessary sample size on the basis of an expected difference of 3% between HBsAg positive rates in patients with diabetes and people without diabetes, with $\alpha=0.05$ and $\beta=0.20$. In each group, 399 participants were required, resulting in 798 total participants.

Patient and public involvement

No patients were involved in the design or conduct of the study. The results were disseminated to study participants through telephone interviews.

Data collection

Questions on the questionnaire were established based on literature review and expertise consultation. After the pilot test, the final version of the questionnaire was developed, comprising information on demographics (sex, age, education, marriage, occupation) and frequency of blood glucose monitoring either at home or in a hospital (including outpatient or inpatient). We confirmed the history of diabetes with patients' medical records. Please refer to online supplemental Appendix A for the detailed questionnaire. After standardised training, experienced investigators conducted a one-to-one questionnaire survey on the participants. Unique identification was the same in both the questionnaire and blood samples, while protecting the privacy of the participants.

Interventions

Senior laboratory technologists collected 5 mL of venous blood sample from participants using sterile disposable vacutainer tube. Left for 30 min to facilitate clotting, the clotted blood was then centrifuged to separate the serum from the blood. The serum was used for HBsAg screening by double-antibody sandwich ELISA at a county laboratory. Diagnostic kit for HBsAg which met the national reference standard was used. The coincidence rate of positive reference was 3/3 and that of negative reference was 20/20. The minimum detection of HBsAg adr, adw and ay of sensitive reference met the requirements. The precision (Coefficient of Variation, CV) was not higher than 15%. The laboratory technologists were blinded to the attribution of the blood sample (people with diabetes or not).

Definition of diabetes status

Referring to the Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2017 Edition),[17] all patients with diabetes were clearly diagnosed by county-level hospitals and had fasting blood glucose level of ≥7.0 mmol/L and haemoglobin A1c level of ≥6.3%. Participants were tested for fasting blood glucose before they were included in the study. When the fasting blood glucose was <7 mmol/L, participants were defined as people without diabetes. Among those without diabetes, people with fasting blood glucose level of 6.1–6.9 mmol/L were defined as having impaired fasting glucose (IFG). People with fasting blood glucose level of ≤6.0 mmol/L were defined as people with normal blood glucose.

Informed written consent was obtained from all participants before the survey. The information was handled with high level of confidentiality and anonymity.

Statistical analysis

Categorical variables were expressed as absolute and relative frequencies in different groups. Patients with diabetes were divided into four groups according to the duration of diabetes. χ^2 test was used to compare the characteristics of patients with diabetes and people without diabetes. Whether HBsAg was positive or not was defined as the dependent variable, and the frequency of blood glucose monitoring and whether diabetes or not were defined as the independent variables in stratified analysis. Sociodemographic characteristics were considered as covariates and were controlled in a stratified analysis. Stratified analysis was used to identify whether frequency of blood glucose monitoring or diabetes mellitus was associated with HBV infection. The frequency of blood glucose monitoring as a non-normal, quantitative variable was compared using Mann-Whitney test. Binary logistic regression analysis was performed to determine if diabetes mellitus was independently associated with HBV infection. OR for logistic regression was calculated with its 95% CI. All tests were two-sided, and p<0.05 was considered significant. Data handling and analysis were performed with SPSS V.24.0.

RESULTS

Characteristics of the study population

The study included 408 patients with diabetes and 408 people without diabetes. There was little difference between patients with diabetes and people without diabetes in terms of sex, age, education, marital status and occupation. The average age of patients with diabetes was 52.3 (SD=8.2) and of people without diabetes was 51.6 (SD=8.1). Both of these groups were mainly aged 51–60 (173 (42.4%) vs 174 (42.7%)), followed by those aged 41–50 (164 (40.2%) vs 164 (40.2%)). The educational level of patients with diabetes (168, 41.2%) and people without diabetes (175, 42.9%) was mainly primary school and below. Most of the subjects were married and employed as farmers (table 1).

Table 1 Characteristics of the study population by diabetes status

	People without diabetes (n=408) (%)	Patients with diabetes (n=408) (%)	χ^2	P value
Sex			0.08	0.78
Male	198 (48.5)	202 (49.5)		
Female	210 (51.5)	206 (50.5)		
Age				
≤40	20 (4.9)	21 (5.1)	0.07	1.00
41–50	164 (40.2)	164 (40.2)		
51–60	173 (42.4)	174 (42.7)		
>60	51 (12.5)	49 (12.0)		
Education			0.63	0.89
College and above	9 (2.2)	9 (2.2)		
Senior high school	70 (17.1)	62 (15.2)		
Junior high school	161 (39.5)	162 (39.7)		
Primary school and below	168 (41.2)	175 (42.9)		
Marriage			5.62	0.06
Married	390 (95.6)	400 (98.0)		
Unmarried	6 (1.5)	5 (1.2)		
Widowed	12 (2.9)	3 (0.8)		
Occupation			0.83	0.84
Farmer	390 (95.6)	387 (94.9)		
Professional skill worker	10 (2.4)	10 (2.4)		
Business staff	4 (1.0)	4 (1.0)		
Other	4 (1.0)	7 (1.7)		

Association between frequency of blood glucose monitoring and HBV infection

The HBsAg positive rate in people without diabetes was 2.0% and in patients with diabetes was 4.2%. We ranked the frequency of blood glucose monitoring (see online supplemental Appendix B) and compared it in people with and without diabetes by stratified analysis. People without diabetes rarely monitored blood glucose at home (median frequency (P_{25}, P_{75})=1 (1, 1)). Among patients with diabetes, the median frequency of SMBG at home was once every 1–3 months.

Mann-Whitney test showed that, whether in people without diabetes or patients with diabetes, higher SMBG frequency was associated with higher HBsAg positive rate (p=0.01 in people without diabetes, p=0.02 in patients with diabetes) (table 2). However, if stratified according to the frequency of SMBG, no association between diabetes and HBV infection was found (p=0.14 among people who had little monitoring at home, p=0.53 among people who did at least one monitoring in a year at home) (table 3). This study did not find a relationship between frequency of blood glucose monitoring in hospital and HBV infection (p=0.13 in people without diabetes, p=0.06 in patients with diabetes) (table 2).

Association between frequency of blood glucose monitoring and diabetes

We compared the frequency of blood glucose monitoring in people with different diabetes states and durations by Mann-Whitney test. Whether blood glucose monitoring at home or in a hospital, there was no significant difference in frequency between people with IFG and those with normal blood glucose (the same median (P_{25}, P_{75})=1 (1, 1) for monitoring at home, median (P_{25}, P_{75})=1 (1, 2)

Table 2 Stratified analysis of the relationship between glucose monitoring and HBV infection stratified by diabetes

		People without diabetes	Patients with diabetes
n		408	408
Number of HBsAg-positive (%)		8 (2.0)	17 (4.2)
Blood glucose monitoring at home	Median (P25, P75)	1 (1, 1)	4 (1, 6)
	Mean rank in people with HBsAg+	273.1	267.7
	Mean rank in people with HBsAg−	203.1	201.8
	Z	−2.7	−2.3
	P value	0.01	0.02
Blood glucose monitoring in hospital	Median (P25, P75)	1 (1, 2)	3 (2, 4)
	Mean rank in people with HBsAg+	261.3	152.9
	Mean rank in people with HBsAg−	203.4	206.7
	Z	−1.5	−1.9
	P value	0.13	0.06

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

for monitoring in hospital), but the frequency in participants with diabetes was higher than the other two groups. In particular, the frequency of SMBG at home in patients with diabetes for more than 10 years (median (P_{25}, P_{75})=5 (4, 6)) was significantly higher than of other patients with diabetes. As the duration of diabetes increased, the frequency of SMBG at home also rose, but there was no difference in the frequency of blood glucose monitoring in hospitals (figure 1).

Association between diabetes mellitus and HBV infection

The HBsAg positive rate in people with normal blood glucose was 1.5% and in people with IFG was 3.5%. Increase in the duration of diabetes correlated with the positivity rate of HBsAg (1.3%, 3.4%, 6.3% and 6.7% respectively; p value of linear-by-linear association=0.01). Compared with people with normal blood glucose, logistic regression identified an association between diabetes and HBV infection (OR=2.8; 95% CI 1.0 to 7.6), but IFG was not (OR=2.3; 95% CI 0.5 to 9.9). Additionally, patients with longer duration of diabetes had a higher OR for HBV infection than those with normal blood glucose, especially those with a duration of more than 6 years (6–9 years of diabetes, OR=4.3, p=0.02; ≥10 years of diabetes, OR=4.5, p=0.02) (table 4).

DISCUSSION

In this study, we used two stratified analyses to explore the relationship between diabetes and HBV infection. Whether in people without diabetes or patients with diabetes, higher SMBG frequency was associated with higher HBsAg positive rate. However, if stratified according to the frequency of SMBG, no association between diabetes and HBV infection was found. These two results indicated that HBV infection may be related directly to SMBG at home, not diabetes. The American Diabetes Association recommends that blood glucose monitoring be used as a necessary requirement for treatment adjustment and glycaemic control in patients with diabetes.[18–20] While blood glucose monitoring was beneficial to patients with diabetes, this increase in the frequency of monitoring also presented certain potential dangers to patients with diabetes. The familial concentration of hepatitis B is common in China. Studies showed that having hepatitis B-positive family members was a risk factor for HBV infection.[21–23] Patients with diabetes often needed to monitor blood glucose and insulin injections frequently, and this study found that there was a dose–response relationship between the duration of diabetes and SMBG at home. Auto-disposal syringes had high

Table 3 Relationship between diabetes and HBV infection stratified by blood glucose monitoring at home

		Among people who had little testing at home (n=502)		Among people who do at least one test a year at home (n=314)	
	n	HBsAg+ (%)	P value*	HBsAg+ (%)	P value*
People without diabetes	408	4 (1.2)	0.14	4 (6.5)	0.53
Patients with diabetes	408	5 (3.2)		12 (4.8)	

*Fisher's exact test.
HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

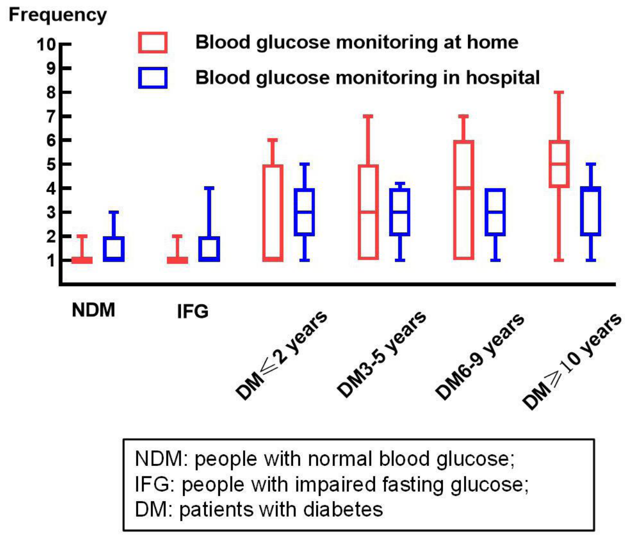

Figure 1 Comparison of frequency of blood glucose monitoring in people with different diabetes status and duration.

potential economic benefits, but auto-disposal syringes and auto-disposal needles are not popular in Chinese families, especially in rural areas, due to higher prices. Blood glucose monitor test papers are disposable, but syringes and needles may be reused, even among different family members, in order to reduce costs. Therefore, unclean SMBG, needle-stick and sharps-related injuries, which occur frequently, would keep patients with diabetes at high risk of HBV infection.[24 25] Studies also reported outbreaks of acute HBV infections during blood glucose monitoring all over the world.[26–31]

In this study, we introduced groups with IFG and with different durations of diabetes. The results showed that the risk of HBV infection in the IFG group was not significantly different from that in the group with normal blood glucose (p=0.25), while the diabetes group was statistically associated with higher HBsAg positive rate than the group with normal blood glucose (OR=2.8, p<0.05). In particular, there was a dose–response relationship between the duration of diabetes and HBV infection. The results suggested HBV infection might be unique to patients with diabetes (especially those with diabetes for more than 6 years), rather than those with blood glucose dysregulation. Compared with people with normal blood glucose, the OR for HBV infection among diabetes was higher than other published studies. Our previous study suggested that there was an association between diabetes and HBV infection; the combined OR of case–control studies was 1.55,[32] while the OR in another meta-analysis was 1.33.[33] In the National Health and Nutrition Examination Survey in the USA, the prevalence of HBV infection in people with diabetes was 60% higher than in those without diabetes.[9]

Interventions on high-risk population is essential to reduce hepatitis B incidence, and patients with diabetes need to be counted. In May 2016, the World Health Assembly adopted the first 'Global Health Sector Strategy on Viral Hepatitis, 2016–2020'[34] with global targets of reducing new viral hepatitis infections by 90% and reducing deaths due to viral hepatitis by 65% by 2030. The hepatitis B vaccine position paper revised by the WHO in 2017 highlighted that the population with diabetes is at high risk of HBV infection.[35] According to unpublished data, less than 40% Chinese people recognised that patients with diabetes are at higher risk of HBV infection, which created obstacles for the promotion of hepatitis B vaccine in high-risk populations. More health education and information popularisation need to be carried out among people with diabetes. When people with diabetes monitor their blood glucose at home, auto-disposal syringes and auto-disposal needles need to be provided at cheaper prices or even for free to avoid sharing of sharps and therefore transmission of HBV.

The results of this research must be considered within the context of its limitations. This study is a cross-sectional survey. It is difficult to exclude the possibility that some subjects were infected with HBV at birth; however, if we matched people with and without diabetes, it would reduce bias to a large extent. A second potential limitation is recall bias because the frequency of blood glucose monitoring was reported by the participants rather than from medical records. Finally, the evidence on SMBG and HBV infection collected in this study was still circumstantial, and potential confounding factors may lead to bias in the association between diabetes and HBV infection; thus, high-quality studies are needed to explore the causal association between them.

Routine blood glucose monitoring at home was associated with HBV infection, which meant people with diabetes may be at high risk of HBV infection. China has a large population with diabetes and sources of HBV infection and hence should develop designated vaccination policy for the population with diabetes to prevent

Table 4 HBsAg positive rate among populations with different diabetes status

	n	HBsAg positive rate (%)	OR (95% CI)	P value
Diabetes status				
NDM	323	1.5	Reference	
IFG	85	3.5	2.3 (0.5 to 9.9)	0.25
DM	408	4.2	2.8 (1.0 to 7.6)	0.05*
Diabetes duration (years)				
≤2	77	1.3	0.8 (0.1 to 7.3)	0.87
3–5	177	3.4	2.2 (0.7 to 7.4)	0.19
6–9	79	6.3	4.3 (1.2 to 15.2)	0.02
≥10	75	6.7	4.5 (1.3 to 16.1)	0.02

*P=0.048<0.05.
DM, patients with diabetes; HBsAg, hepatitis B surface antigen; IFG, people with impaired fasting glucose; NDM, people with normal blood glucose.

HBV infection and achieve the goal of hepatitis control by 2030.

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Patient consent for publication Not required.

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Appendix A

Questionnaire on HBV infections in people with or without diabetes

Informed Consent

There is a survey designed by School of public health, Peking University, aiming to understand the status of diabetes and HBV infection, frequency of monitoring blood glucose. This survey does not involve any privacy or sensitive issues, and the results of the it will be helpful to the management of patients with diabetes in China.

Part A. Relevant information of diabetes

A1. Have you ever been diagnosed with diabetes?

a. Yes

b. No

c. Uncertain

A2. How long have you had diabetes?

________ years

A3. If you have been diagnosed with diabetes, please bring a certificate of diagnosis or fill in the name of a hospital.

____

Part B. Relevant information of HBV infection

B1. Have you ever infected hepatitis B virus before?

a. Yes

b. No

c. Uncertain

B2. Have you ever been vaccinated against hepatitis B before?

a. Yes

b. No

c. Uncertain

B3. If you have been diagnosed with HBV infection, please bring a certificate of diagnosis or fill in the name of a hospital.

____

Part C. The frequency of monitoring blood glucose

C1. How often do you monitor your blood glucose at home?

a. Almost no testing
b. Once every 6-12 months
c. Once every 3-6 months
d. Once every 1-3 months
e. Once every 2-4 weeks
f. Once every 1-2 weeks
g. Once every 3-7 days
h. Once every 1-3 days
i. Once a day
j. Many times a day

C2. How often do you monitor your blood glucose in hospital?

a. Almost no testing
b. Once every 6-12 months
c. Once every 3-6 months
d. Once every 1-3 months
e. Once every 2-4 weeks
f. Once every 1-2 weeks
g. Once every 3-7 days
h. Once every 1-3 days
i. Once a day

j. Many times a day

Part D. Sociodemographic Characteristics

D1. Are you currently living in an urban or rural area?

a. Urban

b. Rural

D2. What is your age?

_______ years old

D3. What was your sex at birth?

a. Male

b. Female

D4. What is your marital status?

a. Never married

b. Engaged or married

c. Separated or divorced

d. Widowed

e. Others

D5. What is your highest level of education?

a. Primary school

b. Junior high school

c. Senior school

d. Some college or a bachelors degree

e. Masters, PhD, or above

D6. What is your main occupation?

a. Labor worker

b. Farmer

c. Teachers and researchers

d. Service/retail

e. Civil servant

f. Health care workers

g. Self-employed

h. Office worker

i. Driver

j. Retired people

k. Student

l. Unemployed

m. Others

Appendix B Rank definition of different frequency of blood glucose monitoring

Rank	Frequency
1	Almost no testing
2	Once every 6-12 months
3	Once every 3-6 months
4	Once every 1-3 months
5	Once every 2-4 weeks
6	Once every 1-2 weeks
7	Once every 3-7 days
8	Once every 1-3 days
9	Once a day
10	Many times a day