

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Han, Bingfeng; Liu, Wu; Yang, Shubo; Wang, Shuai; Du, Juan; Liu, Yaqiong; Cui, Fuqiang

VERSION 1 – REVIEW

REVIEWER	Makuza, Jean Damascene Rwanda Biomedical Center, Institute of HIV, Diseases Prevention and Control
REVIEW RETURNED	16-Feb-2021

GENERAL COMMENTS	<p>This is a good study for the identification of the preliminary relationship between HBV and diabetes. The subject is original and could contribute to the prevention of HBV in different key populations like Patients with diabetes. 408 participants with diabetes and 408 controls are a good sample size that can give appropriate results. However, there is a need to address some gaps in this study:</p> <p>1) Abstract:</p> <p>In objectives, I can see only a hypothesis, please add also the study objectives. You can spell also what does it mean HBV for the first time.</p> <p>In settings, there is a repetition of "comparative cross-sectional" which was presented before in study design.</p> <p>I do not see the Interventions section which is very important in the abstract, please add and describe this section.</p> <p>2) Introduction:</p> <p>Line 81-83: you can precise the period of reporting of these HBV figures.</p> <p>Line 86: Are 86 million people equal to 6,1% of prevalence of HbsAg or these include also occult infection? Please clarify.</p> <p>Line 97: please show the figures of HBV infection in diabetes patients globally, in different countries in the same income setting as China. We need to know also the impact of diabetes on HBV infection as well.</p> <p>There is a need to show the problem of coinfection diabetes and HBV so that you can show the importance of this study.</p> <p>3) Methods</p> <p>Study population:</p> <p>Why did decide to conduct this study in Gansu province? Is there more prevalent diabetes or HBV in China? Please tell the readers the reasons for your choice.</p>
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	<p>As this section contains information about settings, it could be named study population and settings</p> <p>Data collection: Who did data collection (recording patient information on the questionnaire)? Are Senior laboratory technologists who did testing and record all needed information? Were they trained on data collection for this study? There is a need for an interventions section where ELISA could be described (Type of ELISA, sensibility, and specificity), laboratory and lab tech who performed this test. In this section, you could also discuss Diabetes testing for non-diabetic and diabetic participants. Statistical analysis; How did you perform your logistic regression analysis? What variables were included in the final model? What was the process? In table 1, you used Chi-square and this test was not defined anywhere in the method section. I did not see the description of all variables used in your study: Please define your dependent and independent variables.</p> <p>4) Results Characteristics of the study population Line 170: The sample size as it was included in the Abstract study participants could also be in Methods, study participants. Quantitative analysis of participants' age like mean(SD), maximum, minimum age, as well as other dependent variables like sex, marital status,..., could be summarized in results. Before presenting percentage, I suggest presenting also a number of participants.</p> <p>It is known that there are other comorbidities that share the same route of transmission with HBV like HIV, HCV, It could be better also to include them in variables. This could help in learning how self-monitoring of blood glucose has an effect on the acquisition of bloodborne infections. For the Association between the frequency of blood glucose monitoring and HBV infection, I suggest using logistic regression and use all necessary variables for identifying the direction of the association and other predictors, this is applied also to diabetes Mellitus and HBV infections.</p> <p>5) Discussion According to what presented in the discussion part of this study, SMBG is characterized as a confounder for Diabetes and HBV controlled by stratification but it was not presented properly in this part. Please look at how you can address this problem in methods and discussion. In limitation also, the problem of lack of sufficient variables was not declared while several conditions could explain the association between Diabetes and HBV infection in this study. Please try to explore most of them.</p> <p>References: Reference 22, 25, 33 are not updated, you can remove it as the oldest one</p> <p>There is a need to attach the questionnaire used in the data collection</p>
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REVIEWER	Million, Y University of Gondar College of Medicine and Health Sciences, Medical Microbiology
REVIEW RETURNED	03-Mar-2021

GENERAL COMMENTS	<p>Comments to the Author</p> <p>The authors present a study regarding the association between self-monitoring of blood glucose and hepatitis B virus infection among people with diabetes mellitus in Gansu Province, China.</p> <p>General question: the author is trying to associate the self-monitoring of blood glucose and HBV infections. The virus is mainly transmitted through direct contacts with blood and fluid products, and the test is performed using a sterile needle. Therefore, how this self-monitoring could be a factors for having HBV? I wonder if you could brief the biological hypothesis.</p> <p>The second concern is that there are scientific reports that showed the virus could result in diabetes; via the extra-hepatic manifestations leading to Type I DM, and the virus affects the lipid metabolism and predisposes to Type II DM. Hence, how your study could address this 'chick- egg dilemma'.</p> <p>Specific comments:</p> <p>Introduction</p> <p>Line 103: you have stated the gap as "Currently, there is no sufficient evidence to show a causal relationship between diabetes or SMBG and HBV infection in China, which is a country with both high prevalence of HBsAg and diabetes." However, your study was not meant to identify causality. Therefore, it would be better to state the problem that would be addressed by the study.</p> <p>METHODS</p> <p>Line 117: 'People without diabetes were randomly recruited in the 118 same township hospitals, who were eligible for the study if they 1) were no less than 18 years old; 2) need two or more fasting blood glucose tests that were < 7 mmol/L; 3) provided informed consent". I have two questions regarding the inclusion criteria: does informed consent could be considered as eligibility criteria? (I think it is a part of ethical issues and should not be eligibility criteria). The second issue is do you considered vaccination status of the participant for HBV in your questioner? If so do you think that HBV vaccination status should be considered as exclusion criteria?</p> <p>Line 141: HBsAg screening was done using enzyme-linked immunosorbent assay (ELISA).</p> <p>HBV has at least 5 serological markers (HBsAg, anti-HBs, anti-HBc, HBe, anti-HBe), each telling different story about the infection status. HBsAg, which is analysed in this study, becomes undetectable after 6 months following HBV infection except in minority (about 5%) of cases that take chronic course. To be able to assess the risk factors of HBV infection, the authors need to include at least analysis of anti-HBc. Anti-HBc is a marker that remains in the blood for a longer period following infection (may be for the lifetime of the person) and considered to be appropriate to show HBV exposure.</p>
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VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER #1:

We greatly appreciate your constructive suggestions and comments. We have carefully considered the comments and have revised the manuscript.

This is a good study for the identification of the preliminary relationship between HBV and diabetes. The subject is original and could contribute to the prevention of HBV in different key populations like Patients with diabetes. 408 participants with diabetes and 408 controls are a good sample size that can give appropriate results.

However, there is a need to address some gaps in this study:

Comment 1:

1) Abstract:

In objectives, I can see only a hypothesis, please add also the study objectives. You can spell also what does it mean HBV for the first time.

In settings, there is a repetition of "comparative cross-sectional" which was presented before in study design.

I do not see the Interventions section which is very important in the abstract, please add and describe this section.

Response:

Thank you very much for careful check. It is updated now.

Modification:

Refer to Page 2 in Revised Manuscript with Changes Marked, from line 23 to line 30 of the Abstract Objectives: The purpose was to 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: In Gansu Province, China in October, 2018.

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

Interventions: The questionnaire was used to collect data on demographics and frequency of SMBG, and venous blood was collected for HBV serological testing.

Comment 2:

2) Introduction:

Line 81-83: you can precise the period of reporting of these HBV figures.

Line 86: Are 86 million people equal to 6,1% of prevalence of HbsAg or these include also occult infection? Please clarify.

Line 97: please show the figures of HBV infection in diabetes patients globally, in different countries in the same income setting as China. We need to know also the impact of diabetes on HBV infection as well.

There is a need to show the problem of coinfection diabetes and HBV so that you can show the importance of this study.

Response 2:

Thank you very much for careful check. It is updated now.

There are nearly 1.4 billion people in China, so 86 million people are equal to 6,1% of prevalence of HBsAg. "86 million" means number of HBsAg-positive infections in the general population.

In the articles we read, the association between diabetes and acute HBV infection was mainly shown in the articles in the US. There are only a few similar studies in China and South Korea, and there are some limitations, such as small sample size.

a. Refer to Page 4 in Revised Manuscript with Changes Marked, from line 102 to line 104 of the Introduction

In 2015, an estimated 257 million people in the world are living with hepatitis B virus (HBV) infection. Of the adult population in the Western Pacific Region, 6.2% is infected, which is the highest rate among the WHO regions.

b. Refer to Page 4 in Revised Manuscript with Changes Marked, from line 107 to line 108 of the Introduction

.....in 2016, there were 86 million people with HBsAg-positive in China, and the estimated HBsAg prevalence rate was 6.1%.

c. Refer to Page 4 in Revised Manuscript with Changes Marked, from line 118 to line 120 of the Introduction

Studies in the US reported the high risk of acute HBV infection in patients with diabetes, and it showed the higher prevalence of HBsAg in diabetic patients in a few articles.

Comment 3:

3) Methods

Study population:

Why did you decide to conduct this study in Gansu province? Is there more prevalent diabetes or HBV in China? Please tell the readers the reasons for your choice.

As this section contains information about settings, it could be named study population and settings
Response 3:

We chose Gansu Province by convenient sampling. The hospital and CDC of Gansu Province have the cooperation foundation with our research group. Afterwards, the immunogenicity and safety of two major hepatitis B vaccines were evaluated in the basis of this study. That study has been published, please refer to <https://pubmed.ncbi.nlm.nih.gov/33992438/>. In addition, Jingyuan County has a population of approximately 455,000 people living in 18 towns. And 6791 diabetic patients were recorded by 18 township hospitals. It is an ordinary county recommended by local experts, which is representative in Gansu Province.

Refer to Page 4 in Revised Manuscript with Changes Marked, from line 133 to line 136 of the Methods

Study population and settings

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.

Comment 4:

Data collection:

Who did data collection (recording patient information on the questionnaire)? Are Senior laboratory technologists who did testing and record all needed information? Were they trained on data collection for this study?

There is a need for an interventions section where ELISA could be described (Type of ELISA, sensibility, and specificity), laboratory and lab tech who performed this test. In this section, you could also discuss Diabetes testing for non-diabetic and diabetic participants.

Response 4:

Thank you for the suggestion. An interventions section was created. We have enriched some details of the questionnaire and laboratory tests.

Modification:

Refer to Page 5 in Revised Manuscript with Changes Marked, from line 172 to line 194 of the Data collection and Interventions

Data collection

Questionnaire questions were established based on literature review and expertise consultation. After the pilot test, the final version of the questionnaire was developed comprised of 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 Appendix A for detailed questionnaire. After

standardized training, experienced investigators conducted a one-to-one questionnaire survey on the participants. Unique ID was the same in both the questionnaire and blood samples, while protecting the privacy of participants.

Interventions

Senior laboratory technologists collected 5 mL of venous blood sample from participants using sterile disposable vacutainer tube. Left for 30 mins to facilitate clotting, and the clotted blood was centrifuged to separate the serum from the blood. The serum was used for HBsAg screening by double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) at a county laboratory. Diagnostic kit for HBsAg was used which met the national reference standard. 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 (CV) was not higher than 15%. The laboratory technologists were blinded to the attribution of the blood sample (people with diabetes or not).

Comment 5:

Statistical analysis;

How did you perform your logistic regression analysis? What variables were included in the final model? What was the process?

In table 1, you used Chi-square and this test was not defined anywhere in the method section.

I did not see the description of all variables used in your study: Please define your dependent and independent variables.

Response 5:

Due to the use of one-to-one matching, logistic regression did not adjust for other variables. We have supplemented the chi square test and the definitions of independent variable and dependent variable.

Modification:

Refer to Page 6 in Revised Manuscript with Changes Marked, from line 211 to line 221 of the 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. Chi square test was used to compare the characteristics of patients with diabetes and people without diabetes. Whether HBsAg was positive or not was defined as a dependent variable, and the frequency of blood glucose monitoring or whether diabetes was defined as an independent variable. Stratified analysis was used to identify whether frequency of blood glucose monitoring or diabetes mellitus was associated with HBV infection.

Comment 6:

4) Results

Characteristics of the study population

Line 170: The sample size as it was included in the Abstract study participants could also be in Methods, study participants.

Quantitative analysis of participants' age like mean(SD), maximum, minimum age, as well as other dependent variables like sex, marital status,..., could be summarized in results.

Before presenting percentage, I suggest presenting also a number of participants.

Response 6:

Thank you very much for the comments. The sample size calculation process has been supplemented in the methods section. And the number of participants in different characteristics has been supplemented in the results section.

Modification:

a. Refer to Page 5 in Revised Manuscript with Changes Marked, from line 164 to line 168 of the Methods

We used PASS (Power Analysis and Sample Size, Version: 15.0.5, NCSS Statistical Software, US) 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.

b. Refer to Page 7 in Revised Manuscript with Changes Marked, from line 228 to line 236 of the Results

408 patients with diabetes and 408 people without diabetes were included in this study. There was little difference between the patients with diabetes and people without diabetes in sex, age, education, marriage, and occupation. The average age of patients with diabetes was 52.3 (SD=8.2), and that of people without diabetes was 51.6 (SD=8.1). Both these two groups were mainly aged 50-60 (173(42.4%) vs. 174(42.7%)), followed by those aged 40-50 (164(40.2%) vs. 164(40.2%)). The educational level of the 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, employed as farmers (Table 1).

Comment 7:

It is known that there are other comorbidities that share the same route of transmission with HBV like HIV, HCV, It could be better also to include them in variables. This could help in learning how self-monitoring of blood glucose has an effect on the acquisition of bloodborne infections.

For the Association between the frequency of blood glucose monitoring and HBV infection, I suggest using logistic regression and use all necessary variables for identifying the direction of the association and other predictors, this is applied also to diabetes Mellitus and HBV infections.

Response 7:

In the design stage of this study, we hope to reduce the confounding factors between groups through systematically recruiting and matching participants. We consulted statistical experts, who suggested that stratified analysis was necessary. Stratified analysis was used to identify whether frequency of blood glucose monitoring or diabetes mellitus was associated with HBV infection. In this study, whether in people without diabetes or patients with diabetes, higher SMBG frequency was associated with higher HBsAg positive rate. But if stratified according to the frequency of SMBG, no association between diabetes and HBV infection was found. The results indicated that HBV infection may be related directly to SMBG at home, not diabetes. The frequency of blood glucose monitoring is a non-normal, quantitative variable, so Mann-Whitney's test should be used to compared it in different groups.

Comment 8:

5) Discussion

According to what presented in the discussion part of this study, SMBG is characterized as a confounder for Diabetes and HBV controlled by stratification but it was not presented properly in this part. Please look at how you can address this problem in methods and discussion.

In limitation also, the problem of lack of sufficient variables was not declared while several conditions could explain the association between Diabetes and HBV infection in this study. Please try to explore most of them.

Response 8:

Maybe our words have caused some misunderstanding to readers. The frequency of SMBG is not a confounder for Diabetes and HBV controlled by stratification. In this study, we made two stratified analysis. On one hand, if stratified according to whether people with diabetes or not, higher SMBG frequency was associated with higher HBsAg positive rate. On the other hand, 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. Some studies on acute HBV infection can support the conclusion of this study.

The existence of potential confounding factors was one of the limitations of this study. In the limitation section, we discussed that “the evidence for SMBG and HBV infection collected in this study was still circumstantial; thus, high-quality studies are needed to explore the causal association between them”.

Modification:

a. Refer to Page 8 in Revised Manuscript with Changes Marked, from line 286 to line 291 of the Discussion

In this study, we used the two stratified analysis 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. But 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.

b. Refer to Page 10 in Revised Manuscript with Changes Marked, from line 344 to line 348 of the Discussion

Finally, the evidence for SMBG and HBV infection collected in this study was still circumstantial, and potential confounding factors may lead to a bias in the association between diabetes and HBV infection; thus, high-quality studies are needed to explore the causal association between them.

Comment 9:

References:

Reference 22, 25, 33 are not updated, you can remove it as it the oldest one

There is a need to attach the questionnaire used in the data collection.

Response 9:

We think your suggestions are very helpful. We have removed these three references, and we attached the questionnaire used in the data collection.

RESPONSE TO REVIEWER #2:

We greatly appreciate your constructive suggestions and comments. We have carefully considered the comments and have revised the manuscript. Please refer to our responses and changes below.

The authors present a study regarding the association between self-monitoring of blood glucose and hepatitis B virus infection among people with diabetes mellitus in Gansu Province, China.

Comment 1:

General question: the author is trying to associate the self-monitoring of blood glucose and HBV infections. The virus is mainly transmitted through direct contacts with blood and fluid products, and the test is performed using a sterile needle. Therefore, how this self-monitoring could be a factors for having HBV? I wonder if you could brief the biological hypothesis.

Response 1 :

Thank you for the valuable point. When monitoring blood glucose in Chinese hospitals, doctors use disposable clean needles. In this study, we did not find the correlation between the frequency of blood glucose monitoring and HBV infection.

China has not only the most carriers of HBsAg, but also the most 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. When monitoring blood sugar at home, diabetic patients may share needles and insulin syringes with others, which increases the risk of HBV transmission. We have found some articles to support this hypothesis. Please refer to the discussion.

Comment 2:

The second concern is that there are scientific reports that showed the virus could result in diabetes; via the extra-hepatic manifestations leading to Type I DM, and the virus affects the lipid metabolism and predisposes to Type II DM. Hence, how your study could address this ‘chick- egg dilemma’.

Response 2 :

Thank you for the professional point. Firstly, as far as this study is concerned, the results have implications for proving the relationship between the frequency of blood glucose monitoring and HBV infection. However, based on the limitations of cross-sectional studies, we can not prove the causal relationship between diabetes and HBV infection. Secondly, A number of cross-sectional studies in many countries show the association between diabetes and HBV infection. But two cohort studies with HBV infection as an exposure factor showed that there was no effect of HBV infection on diabetes development^{1,2}, which may showed a chronological order.

In our opinion, the two logical relations are real. On one hand, HBV could result in diabetes via interference with lipid metabolism. On the other hand, people with routine blood glucose monitoring at home was associated with HBV infection, which meant people with diabetes may be at high risk for HBV infection. This study pays more attention to the latter, but does not oppose the former. High-quality studies are needed to explore the causal association between them.

1. Spradling PR, Simons B, Narayanan M, et al. Incidence of diabetes mellitus in a population-based cohort of persons with chronic hepatitis B virus infection. *J Viral Hepat* 2013;20(7):510-3. doi: 10.1111/jvh.12071

2. Huang ZS, Huang TS, Wu TH, et al. Asymptomatic chronic hepatitis B virus infection does not increase the risk of diabetes mellitus: a ten-year observation. *Journal of gastroenterology and hepatology* 2010;25(8):1420-5. doi: 10.1111/j.1440-1746.2010.06268.x

Comment 3:

Introduction

Line 103: you have stated the gap as “Currently, there is no sufficient evidence to show a causal relationship between diabetes or SMBG and HBV infection in China, which is a country with both high prevalence of HBsAg and diabetes.” However, your study was not meant to identify causality. Therefore, it would be better to state the problem that would be addressed by the study.

Response 3:

We apologize for this misunderstanding. There is not enough evidence to prove causal inference in this study, but we provide a possibility to study the relationship between diabetes and HBV infection, which is to monitor blood glucose at home. In order to eliminate the misunderstanding, we revised this paragraph.

Modification:

Refer to Page 4 in Revised Manuscript with Changes Marked, from line 124 to line 130 of the Introduction

Currently, there is no sufficient evidence to show an association between SMBG and HBV infection in China. Based on both high prevalence of HBsAg and diabetes, A hypothesis established in this study was that SMBG may be an important part of HBV infection in diabetic patients. 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 for the relationship between diabetes and HBV infection.

Comment 4:

METHODS

Line 117: ‘People without diabetes were randomly recruited in the 118 same township hospitals, who were eligible for the study if they 1) were no less than 18 years old; 2) need two or more fasting blood glucose tests that were < 7 mmol/L; 3) provided informed consent’. I have two questions regarding the inclusion criteria: does informed consent could be considered as eligibility criteria? (I think it is a part of ethical issues and should not be eligibility criteria). The second issue is do you considered vaccination status of the participant for HBV in your questioner? If so do you think that HBV vaccination status should be considered as exclusion criteria?

Response 4:

In fact, we investigated the history of hepatitis B vaccination among participants, but it's for the further research, not for this study. We believe that hepatitis B vaccination should be random in people with and without diabetes, so we did not include it in the exclusion criteria. We do not intend to disclose the

distribution of hepatitis B vaccination in the two groups in this article, but we give the result here to provide reference for reviewers. We did not find statistical differences in hepatitis B vaccination between the two groups ($\chi^2=4.314$; $P=0.116$).

	Vaccinated	No vaccination	Uncertain	Total
Patients with diabetes	109	278	21	408
People without diabetes	84	303	21	408
Total	193	581	42	816

$\chi^2=4.314$; $P=0.116$

Comment 5:

Line 141: HBsAg screening was done using enzyme-linked immunosorbent assay (ELISA). HBV has at least 5 serological markers (HBsAg, anti-HBs, anti-HBc, HBe, anti-HBe), each telling different story about the infection status. HBsAg, which is analysed in this study, becomes undetectable after 6 months following HBV infection except in minority (about 5%) of cases that take chronic course. To be able to assess the risk factors of HBV infection, the authors need to include at least analysis of anti-HBc. Anti-HBc is a marker that remains in the blood for a longer period following infection (may be for the lifetime of the person) and considered to be appropriate to show HBV exposure.

Response 5:

Thank you for the valuable point. We took this point into account in the study design stage. Hepatitis B surface antigen (HBsAg) is a blood test ordered to determine if someone is infected with the hepatitis B virus. If the blood is positive for HBsAg, it means it is infectious for the virus and can pass HBsAg to other people through the blood or body fluids. In order to study the possibility of HBV transmission in people with and without diabetes, this study is more concerned about HBsAg positive. However, we think that this comment is very helpful. We will consider other serological markers into the next study.

VERSION 2 – REVIEW

REVIEWER	Makuza, Jean Damascene Rwanda Biomedical Center, Institute of HIV, Diseases Prevention and Control
REVIEW RETURNED	30-Jun-2021

GENERAL COMMENTS	<p>There is improvement in this version comparably to the former one but there are still some gaps to fill as follows:</p> <p>1) ABSTRACT Objectives: page 29, line 24: "the purpose was to the association...." I think there a missing word to complete the sentence Setting: line 30, I think you have to explain in summary if the study was conducted in a hospital or in the community. Interventions: I think the 1st sentence of this part is the data collection process, I may delete "The questionnaire was used to collect data on demographics and 34frequency of SMBG, and" and develop venous blood collected and HBV testing as well as blood glucose testing.</p> <p>2) METHODS: Page 35, line 189-190, among independent variables, you could include socio-demographic characteristics which are described in results like age, sex, education,...</p>
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VERSION 2 – AUTHOR RESPONSE

RESPONSE TO REVIEWER #1:

We greatly appreciate your constructive suggestions and comments. We have carefully considered the comments and have revised the manuscript.

There is improvement in this version comparably to the former one but there are still some gaps to fill as follows:

Comment 1:

1) ABSTRACT

Objectives: page 29, line 24: "the purpose was to the association...." I think there a missing word to complete the sentence.

Response:

Thank you very much for careful check. We apologize for the lack of a verb. It is updated now.

Modification:

Refer to Page 2 in Revised Manuscript with Changes Marked, from line 23 to line 25 of the Abstract

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

Comment 2:

Setting: line 30, I think you have to explain in summary if the study was conducted in a hospital or in the community.

Response 2:

Thank you very much for careful check. It is updated now.

Refer to Page 2 in Revised Manuscript with Changes Marked, from line 27 of the Abstract

Setting: In 6 township hospitals in Gansu Province, China in October, 2018.

Comment 3:

Interventions: I think the 1st sentence of this part is the data collection process, I may delete "The questionnaire was used to collect data on demographics and 34frequency of SMBG, and" and develop venous blood collected and HBV testing as well as blood glucose testing.

Response 3:

Thank you for the valuable suggestions. We agree with you.

Refer to Page 2 in Revised Manuscript with Changes Marked, from line 30 to line 32 of the Abstract

Interventions: The questionnaire was used to collect data on demographics and frequency of SMBG, and Venous blood was collected for HBV serological testing and blood glucose testing.

Comment 4:

2) METHODS:

Page 35, line 189-190, among independent variables, you could include socio-demographic characteristics which are described in results like age, sex, education,...

Response 4:

In the study design, we have taken into account the balance of sociodemographic characteristics between the two groups. In the stratified analysis, we also took the sociodemographic characteristics as covariates to ensure that the correlation between independent variables and dependent variables was compared after controlling all covariates. We agree with you and have clearly added the description of covariates in the method section.

Modification:

Refer to Page 7 in Revised Manuscript with Changes Marked, from line 164 to line 169 of the Statistical Analysis

Whether HBsAg was positive or not was defined as a dependent variable, and the frequency of blood glucose monitoring or whether diabetes was defined as an independent variable. Sociodemographic characteristics were considered as covariates and were controlled in stratified analysis. Stratified analysis was used to identify whether frequency of blood glucose monitoring or diabetes mellitus was associated with HBV infection.