

Decompensated islet beta cell function in patients with chronic hepatitis B: a retrospective case-control study

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Research article

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Abstract

Background Dysglycometabolism is often accompanied with decreased islet β cell function based on the homeostasis model assessment of β cell function (HOMA- β). In this study, we aimed to identify the difference in HOMA- β values between Chronic hepatitis B (CHB) and non-hepatitis B virus (non-HBV) patients. **Methods** The study included 110 CHB and 110 non-HBV patients matched according to gender, age, and body mass index. HOMA- β values were evaluated. **Results** Under the normal glucose tolerance (NGT) condition, the HOMA- β value of the CHB group was in the decompensated stage, and HOMA- β value of CHB was always lower than non-HBV patients (NGT, impaired glucose regulation, and diabetes mellitus: 47.53 vs. 124.19, 41.59 vs. 80.17, and 36.46 vs. 62.92 mIU/mmol; $t = -4.709, -2.042, \text{ and } -2.091$; $P = 0.000, 0.047, \text{ and } 0.046$, respectively). **Conclusion** Clinicians should focus on dysglycometabolism of patients with CHB.

Background

Chronic hepatitis B (CHB) has affected about 300 million people worldwide¹, of whom about 650,000 die of hepatic failure, liver cirrhosis (LC), and hepatocellular carcinoma (HCC) annually². China is one of the HBV middle- and low-endemic areas worldwide, approximately 93 million people are infected with HBV, among them, 20 million present with CHB^{1,3}.

Although the relationship between hepatitis B virus (HBV) infection and diabetes mellitus (DM) remains unclear, several studies have shown that the prevalence of DM is significantly high in the HBV-infected population^{4,5}, particularly in those with high viral load, long duration of CHB, cirrhosis^{4,6,7}, and Asian Americans⁸. Our previous study has shown that 59.09% of CHB patients have high homeostasis model assessment of insulin resistance (HOMA-IR) values and that 93.64% of individuals have low homeostasis model assessment of β cell function (HOMA- β) value. Moreover, 35.45% of individuals have impaired glucose tolerance (IGT)⁹⁻¹¹, which indicated that the prevalence of dysglycometabolism and insulin resistance (IR) is high in patients with CHB.

IR can promote the progression of liver fibrosis and cirrhosis¹²⁻¹⁵. Moreover, IR is independently correlated to the degree of liver fibrosis in patients with abnormal glutamyltransferase level, which is not associated with the etiology of liver diseases^{9,12,13}. The higher HOMA-IR value, the higher liver stiffness measurement, indicating liver fibrosis^{10,11,14,15}. In patients with cirrhosis and DM, the main cause of death is hepatic failure, not the complications of DM. Furthermore, T2DM can promote HCC and lead to poor prognosis of liver transplantation¹⁵. Therefore, the coexistence of dysglycometabolism and IR can promote the progression and worsen the prognosis of CHB.

Dysglycometabolism and IR are commonly associated with islet β cell dysfunction in the general population, particularly in Asian populations. The HOMA- β value of patients with CHB under normal glucose tolerance (NGT) condition, the changes in HOMA- β value with the deterioration of glycometabolism, and the differences in HOMA- β value between CHB and patients without hepatitis B

virus infection(non-HBV) worth much research. This study aimed to investigate the HOMA- β value of individuals with CHB under NGT condition, the difference in HOMA- β value between CHB and non-HBV patients, and changes in HOMA- β value with the deterioration of glycometabolism.

Methods

Study population

A retrospective case-control study was conducted on 220 patients from the Public and Health Clinic Centre of Chengdu from January 1, 2012 to June 30, 2013. Among them, 110 patients with CHB were included in the CHB group, and the source of the case is in the literature⁹⁻¹¹. Moreover, 110 patients without hepatitis B virus, hepatitis c virus(HCV) and human immunodeficiency virus infection who were matched according to gender, age and body mass index(BMI) were included in the non-HBV group.

The inclusion criteria of the CHB group were as follows: (1)outpatients or inpatients with CHB or post-hepatitis B cirrhosis; (2)those who agreed to undergo noninvasive ultrasound elastometry of the liver; and (3)those aged 18–70 years.

The selection criteria of the non-HBV group were as follows: patients without hepatitis B virus infection who were matched according to gender, age, and BMI.

The following exclusion criteria were used in this study: (1)individuals with other hepatitis virus or human immunodeficiency virus infection; (2)hepatocellular carcinoma; (3)ascites; (4)decompensated cirrhosis; (5)hepatic function alanine aminotransferase(ALT) or aspartate aminotransferase(AST) level higher than the 5-fold upper limit of the normal value, total bilirubin level higher than the 2-fold upper limit of the normal value within the last 6 months, or prothrombin activity (PT%)<60%; and (6)BMI>30 kg/m² or <18.5kg/m².

The diagnostic criteria of the diseases were as follows: CHB diagnostic and typing criteria and IGR and DM diagnostic criteria^{16,17}.

The participants were divided in three subgroups according to glycometabolism conditions: the NGT group [fasting plasma glucose(FPG) level <6.0mmol/L and 2-h postprandial glucose(2hPG) level <7.8mmol/L], IGR group (FPG and 2hPG levels all between that in the NGT and DM), and DM group (FPG level \geq 7.0mmol/L and 2hPGlevel \geq 11.1mmol/L or twice than that of the FPG or 2hPG levels meeting the criteria).

Clinical data collection

Data, which included demographic information(age and sex), anthropometric parameters(body weight and height), glucose metabolic parameters[FPG, 2hPG, fasting insulin (FINS), 2hINS, and hemoglobinA1c(HbA1c) levels] were obtained. BMI, HOMA-IR value, and HOMA- β value were calculated

using the following formulas: $BMI = \text{weight}(\text{kg}) / \text{height}(\text{m}^2)$, $HOMA-IR = \text{fasting plasma insulin (Um/L)} \times \text{FPG (mmol/L)} / 22.5$, and $HOMA-\beta = 20 \times \text{fasting plasma insulin (Um/L)} / [\text{FPG (mmol/L)} - 3.5]^{18}$.

Databases were established according to the needs of the research. Two researchers simultaneously collected and entered the data. The researchers randomly selected 30% of the data for assessment to ensure data integrity, authenticity, and accuracy.

Statistical analyses

The Statistical Package for the Social Sciences software version 17.0 (IBM Inc., Armonk, NY, the USA) and GraphPad Prism 8 (GraphPad) software were used for statistical analysis. Age, BMI, FPG, FINS levels, and HOMA-IR value had a normal distribution, and statistical analysis was conducted directly. Natural HOMA- β values are logarithmic transformation before statistical analysis. The measurement data were expressed as $\bar{x} \pm \text{SD}$, and a multigroup comparison was performed using ANOVA. Further comparison between the two groups was conducted using Student-Newman-Keuls (SNK) analysis. The two groups were compared using an independent-sample t -test. Chi-square test was used for the enumeration data. A p value of <0.05 was considered statistically significant.

Results

Similar baseline conditions between the two groups

No significant difference was observed in terms of age, sex, BMI and glycometabolism conditions between the two groups. Therefore, the baseline condition of the two groups was comparable (Table 1). In the CHB group, 41 (37.27%) patients presented with LC. In the non-HBV group, there was no case of LC.

Decompensated HOMA- β function under NGT condition in the CHB group

Under NGT condition in the non-HBV group, the HOMA- β value (124.19 mIU/mmol) was higher than the normal value (100.00 mIU/mmol). On the contrary, under the same condition, the value (47.53 mIU/mmol) was lower than the normal value in the CHB group. In non-HBV groups and the normal value, the HOMA- β value in the CHB group decreased up to 77.79 and 53.47 mIU/mmol, respectively; therefore, their reducing percentages were up to 62.64% and 53.47%, respectively. The difference was significant (Figure 1A). Under NGT condition, the FINS level and HOMA-IR value of the CHB group were lower than those of the non-HBV group, and the result was significantly different (Figures 1B and 1D). Although FPG level of the CHB group was slightly higher than that of the non-HBV group, no significant difference was observed (Figure 1C).

Decrease in HOMA- β function along with the deterioration of glycometabolism in individuals with CHB

With the deterioration of glycometabolism under NGT, IGR and DM conditions in the two groups, the FPG level and HOMA-IR value (Figure 2A and 2C) increased gradually, and the FINS level slightly increased (Figure 2B). However, the HOMA- β value decreased gradually (Figure 2D). In the non-HBV group,

the HOMA-IR and HOMA- β values were higher under the same glycometabolism condition (regardless if NGT, IGR, or DM) (Figures 2C and 2D), and the FPG level was lower in the non-HBV patients group than in CHB group (Figure 2A). Excluding the FPG level under NGT condition and HOMA-IR value under IGR condition, significant differences were observed, particularly in the HOMA- β value under NGT condition and the FINS level, the HOMA-IR value, the FPG level under DM condition. In the non-HBV group, under IGR and DM condition, the FPG level was <6.0 mmol/L. However, in the CHB group, the FPG level was higher than 6.0 mmol/L under IGR condition and 7.0 mmol/L under DM condition.

In the intragroup comparison of FPG levels under NGT, IGR, and DM conditions between the two groups, significant differences were observed in terms of FINS levels, HOMA-IR value, and HOMA- β value in the CHB group (all $p < 0.0001$) and HOMA- β value in the non-HBV group ($p < 0.05$).

Discussion

Previous studies have shown that the HOMA- β value of patients newly diagnosed with T2DM was only half of the normal value, and it decreased progressively at a rate of 4.5% annually and deteriorated with the course of the disease¹⁹. Therefore, the HOMA- β value of CHB patients under NGT condition was lower than that of non-HBV patients who were newly diagnosed with T2DM.

A new staging method for NGT, IGR, and DM was proposed according to the function of β cells: normal phase of β cell function, compensatory phase of β cell function, decompensated phase of β cell function, and failure phase of β cell function in the general population. The compensatory secretion of β cell function occurs in individuals with NGT and IR and reaches the peak of compensatory secretion. The decompensation of β cell function has occurred in individuals with prediabetes²⁰. In recent years, most studies have confirmed that not all individuals with NGT were healthy and that some presented with IR²¹. The risk of developing prediabetes and/or T2DM significantly increased in individuals with NGT, but not in those with IR and dysfunction of β cell secretion²².

However, the β cell function of the CHB population will directly go to decompensated and failure phases, without undergoing normal and compensatory phases, even under NGT condition, and this phenomenon leads to higher FPG levels and high prevalence of IGR and DM in the CHB population. The evident increase in the FPG level in CHB patients was associated with worsening β cell function compared with non-HBV patients but with similar glycometabolism status.

Generally, in patients with CHB, the HOMA- β value gradually decreased and the FPG level gradually increased along with the deterioration of glucose metabolism. Therefore, the comparison of HOMA- β value between CHB and non-HBV patients was conducted under similar glucose metabolism conditions.

Previous studies have found that chronic liver inflammation and fibrosis caused by HBV infection are associated with some indicators of glycometabolism: CHB patients with mild liver dysfunction had high serum insulin levels and HOMA-IR values. A correlation analysis has shown that ALT was positively correlated to IR. However, HBV DNA load was not correlated to IR. A regression analysis has indicated that

ALT was an independent risk factor of IR in patients with mild liver dysfunction^{23,24}. A pathological study has found that the FINS level and HOMA-IR value of CHB patients with G3 grade inflammation are higher than those of patients with G2 grade inflammation, and the FINS level and HOMA-IR value of CHB patients with S3 grade fibrosis are higher than those of patients with S2 grade fibrosis. Moreover, HOMA-IR was positively correlated to ALT²⁵. When the duration of HBV is longer, patients are more likely to develop IR and abnormal glucose metabolism^{10,11}. When glutamic transpeptidase (GGT) is less than the 1.5-fold upper limit of the normal value, IR is not observed. When the value is 1.5–2 fold than the upper limit of the normal value, IR is most significant. However, it decreases with the increase in GGT level²⁶. The secretory function of islet β cells in patients with hepatitis B cirrhosis is normal, and IGT to a certain extent is observed. In CHB patients, the secretory function of islet β cells decreased significantly⁹. In particular, when the GGT level is 1.5–2 times higher than the normal value²⁶, the steady-state model had the lowest HOMA- β value, with an average of only 20.34 mIU/mmol. With the increase in GGT level, the HOMA- β value was more likely to increase²⁶.

Fundamental studies have found that HBV infection can increase the production of tumor necrosis factor (TNF). The overproduction of TNF can decrease the phosphorylation of insulin receptor substrates 1 and 2, inhibit phosphoinositol 3-kinase and protein kinase B, block the phosphorylation of glucose transporter 4, and prevent the cell uptake of glucose^{27,28} and increase in blood glucose level. Prostate six-transmembrane protein 2 (STAMP2) is a factor associated with inflammation and dietary adipocyte function and system metabolism. It can be induced by nutrition, feeding, and cytokines, such as TNF α , interleukin (IL)-1 β , and IL-6, which can inhibit IR in rats. IR and visceral and hepatic insulin signaling disorders were observed in mice lacking STAMP2. In the presence of inflammation and obesity, the increased expression of STAMP2 has protective effects against insulin signaling in the liver²⁹. Moreover, HBV X protein induces liver fat accumulation and IR by reducing the expression of STAMP2. STAMP2 down-regulates the insulin-induced phosphorylation of P3K p85 subunit and protein kinase and the expression of insulin receptor substrate 1, and the post-transcriptional level of insulin receptor substrate 1 plays a role³⁰, which leads to the increase in blood glucose levels.

Although basic studies have confirmed that HBV infection can lead to increased hepatic glucose output and IR, it cannot explain the decrease in HOMA- β value and FINS level. Further basic studies have indicated that HBV infection affects the function of islet cells in CHB patients.

This case-control study first compared the differences in HOMA- β value and FPG level between CHB patients and non-HBV patients matched according to gender, age and BMI. Results showed that the HOMA- β value of CHB patients was significantly lower than that of non-HBV patients under NGT and the normal value, and was lower than that of non-hepatitis B patients under the same glycometabolism condition. However, the FPG level of CHB patients was significantly higher than that of non-hepatitis B patients.

The present study had some limitations. The sample size was small, and a single-center and retrospective study, rather than a multicenter and prospective study, was conducted.

Conclusions

These findings may provide a guide for clinicians to develop hypoglycemic regimens for patients with CHB and dysglycometabolism. During drug selection, clinicians should focus on protection of islet β cell function and prevention of the use of insulin secretagogues.

List Of Abbreviations

HBV Hepatitis B virus

FINS Fasting insulin

IR Insulin resistance

TNF Tumor necrosis factor

ALT Alanine aminotransferase

BMI Body mass index

CHB Chronic hepatitis B

DM Diabetes mellitus

FPG Fasting plasma glucose

GGT Glutamic transpeptidase

HCC Hepatocellular carcinoma

IGT Impaired glucose tolerance

LC Liver cirrhosis

NGT Normal glucose tolerance

2hPG 2-h postprandial glucose

HOMA- β Homeostasis model assessment of β cell function

IR Insulin resistance

AST Aspartate aminotransferase

FINS Fasting insulin

HbA1c Hemoglobin A1c

Declarations

Ethics approval and consent to participate:

The study was approved by the ethics committee of the Public and Health Clinic Centre of Chengdu. All patients provided a written informed consent.

Consent for publication:

Not applicable

Availability of data and materials:

Not applicable

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

Concept and design: Dafeng Liu, Lingyun Zhou, Xinyi Zhang, Lang Bai, Dongbo Wu; Data acquisition: Dafeng Liu, Lingyun Zhou, Xinyi Zhang; data analysis and interpretation: Dafeng Liu, Lingyun Zhou, Xinyi Zhang, Lang Bai; Drafting the manuscript: Dafeng Liu, Lingyun Zhou, Xinyi Zhang; administrative, technical, or material support: Dafeng Liu, Lingyun Zhou, Xinyi Zhang; study supervision: Yilan Zeng and Hong Tang.

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Table

Table 1. Baseline comparison between the two groups (n=220)

Variables	CHB group(n=110)	Non-HBV group(n=110)	<i>t</i> score or x ² score	Pscore
Age(years)	43.86±14.38	42.68±13.34	<i>t</i> =0.794	0.428
Male(case,%)	90(81.92%)	90(81.92%)	x ² =0.000	1.000
BMI(kg/m ²)	22.52±2.74	23.14±4.07	<i>t</i> =−1.245	0.215
Glycometabolism conditions			x ² =0.000	1.000
NGT	50(45.46%)	50(45.46%)		
IGR	30(27.27%)	30(27.27%)		
DM	30(27.27%)	30(27.27%)		

Abbreviations: CHB, chronic hepatitis B; non-HBV, without hepatitis B virus infection; BMI, body mass index; NGT, normal glucose tolerance; IGR, impaired glucose regulation; DM, diabetes mellitus.

Figures

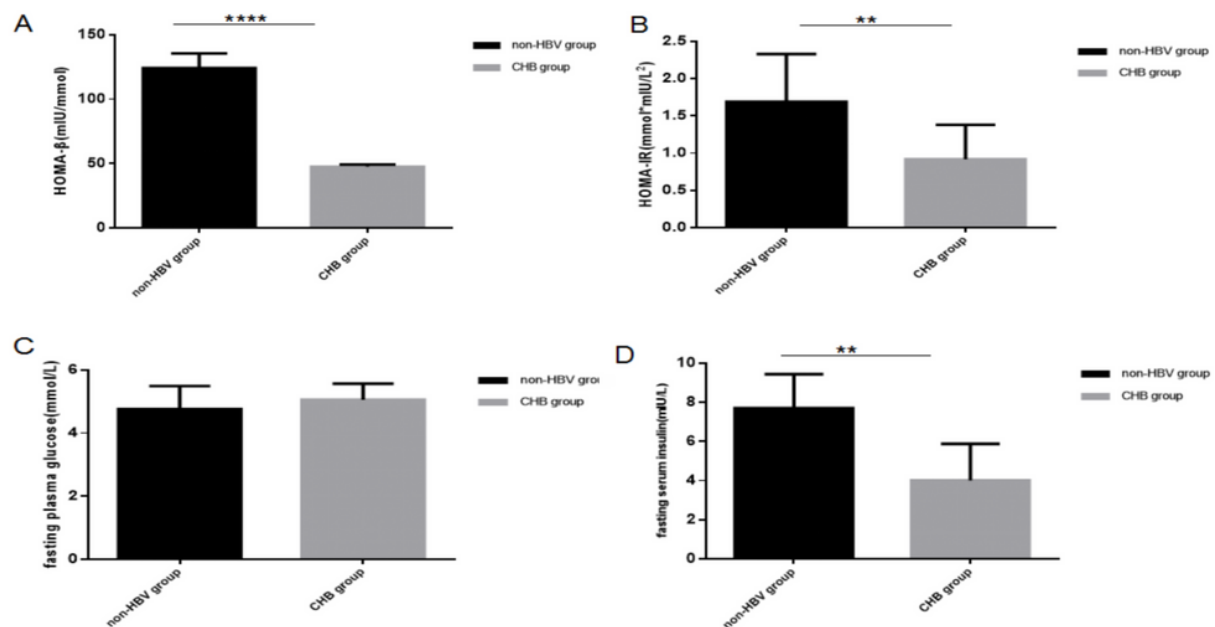


Figure 1

Comparison of the metabolic parameters between the two groups under NGT condition (n=100; CHB group, n=50, non-HBV group, n=50). A. HOMA- β value under NGT condition; B. HOMA-IR value under NGT condition; C. FPG level under NGT condition; D. FINS level under NGT condition. Abbreviations: FPG, fasting plasma glucose; FINS, fasting serum insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA- β , homeostasis model assessment of β cell function; NGT, normal glucose tolerance; CHB, cirrhosis hepatitis B; non-HBV, without hepatitis B virus infection. Matched and unmatched t-tests were used for the intergroup comparison. * $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$.

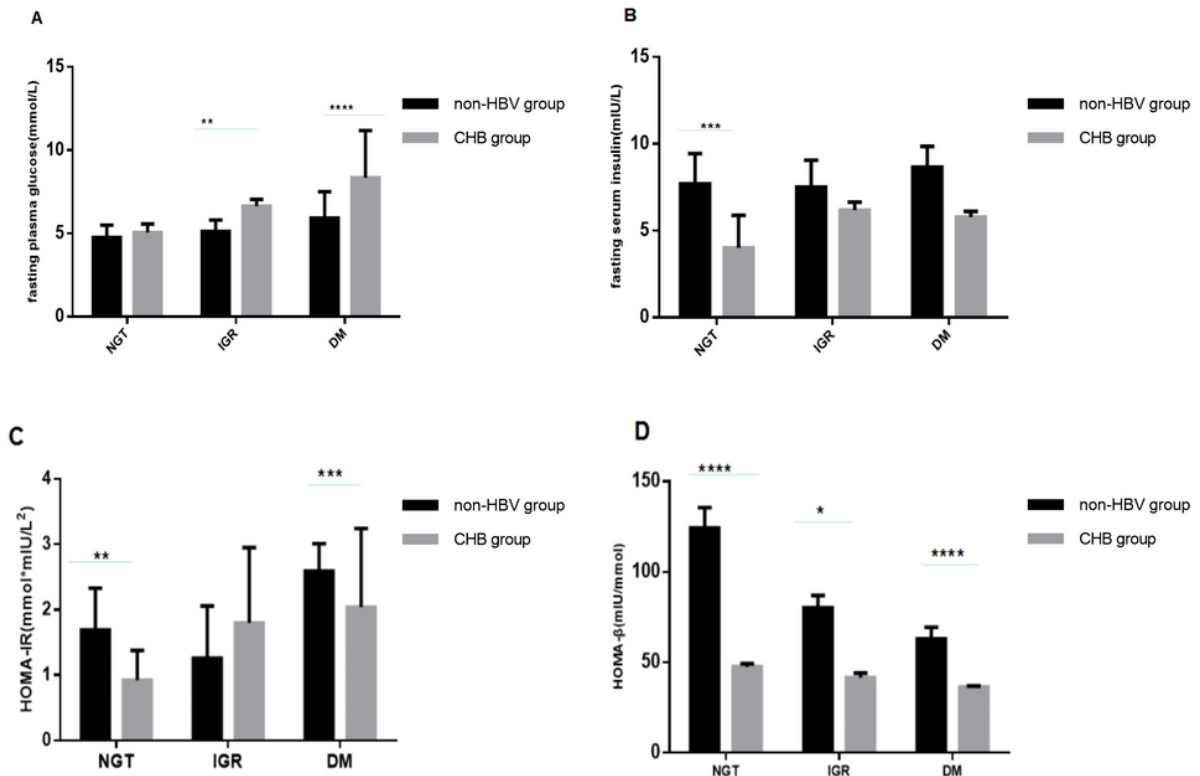


Figure 2

Comparison of the metabolic parameters between the two groups under NGT, IGR and DM conditions (n=220; NGT, IGR, and DM in the two groups, n=50, 30 and 30, respectively). A. FPG levels; B. FINS levels; C. HOMA-IR value; D. HOMA-β value. Abbreviations: FPG, fasting plasma glucose. FINS, fasting serum insulin. HOMA-IR, homeostasis model assessment of insulin resistance HOMA-β, homeostasis model assessment of β cell function; NGT, normal glucose tolerance; IGR, impaired glucose regulation; DM, diabetes mellitus. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001.