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Original Article

Correlation of chronic hepatitis B complicated with or without diabetes mellitus, in patients with insulin resistance, liver damage, and inflammation

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Abstract: *Objective:* The goal of this study was to analyze correlation of chronic hepatitis B complicated with diabetes mellitus, in patients with insulin resistance, liver damage, and inflammation, and to explore the predictive value of risk factors for chronic hepatitis B complicated with diabetes mellitus in patients. *Methods:* A total of 80 patients definitely diagnosed with chronic hepatitis B in our hospital from May 2016 to July 2017 were selected. Among them, 35 complicated with diabetes mellitus were included as the observation group, and 45 patients not complicated with diabetes mellitus were included as the control group, including 50 males and 30 females. Through the collection of the patient's general data, including age, gender, course of chronic hepatitis B, weight, and height, blood lipids, fasting plasma glucose (FPG), fasting serum insulin (FINS), liver function indexes [alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT)], inflammatory cytokines [C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6)], hyaluronic acid (HA), type III protein and type IV protein were determined. The insulin resistance index was also calculated. Moreover, differences in indexes between patients complicated with diabetes mellitus and those not complicated with diabetes mellitus were compared, and their relationships and influencing factors were explored. *Results:* 1) There were no statistically significant differences in age, gender, course of disease, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) between the observation group and the control group ($P > 0.05$), but body mass index (BMI) of the observation group was higher than that of the control group ($P < 0.05$). 2) The levels of FINS, FPG, homeostasis model of assessment for insulin resistance (HOMA-IR), and hemoglobin A1c (HbA1c) in the observation group were remarkably higher than those in the control group, showing statistically significant differences ($P < 0.05$). 3) Comparison of liver function between the two groups revealed that the levels of serum ALT, AST, and GGT in the observation group were higher than those in the control group, with statistically significant differences ($P < 0.05$). 4) In terms of liver fibrosis-related indexes, the levels of serum HA, type III collagen (III-C), and type IV collagen (IV-C) in the observation group were significantly higher than those in the control group ($P < 0.05$). 5) The levels of inflammatory cytokines, including CRP, TNF-α, IL-6 in the observation group were higher than those in the control group, and the differences were statistically significant ($P < 0.05$). 6) Correlation analyses of insulin resistance index, inflammatory cytokines, liver function indexes, and plasma glucose demonstrated that insulin resistance index ($r = 0.757$, $P < 0.001$), ALT ($r = 0.659$, $P < 0.001$) and CRP ($r = 0.603$, $P < 0.001$) were positively correlated with FPG. *Conclusion:* Insulin resistance, liver damage degree and inflammation response degree in the body are closely related to chronic hepatitis B complicated with diabetes mellitus, and affect the severity of diabetes mellitus.

Keywords: Chronic hepatitis B, diabetes mellitus, insulin resistance, liver function inflammatory response

Introduction

Among various causes of chronic liver disease, virus infection is the most common. In China, chronic hepatitis B virus infection accounts for the vast majority. According to relevant data, there are more than 6% of the patients with chronic hepatitis B virus infection in the world, in which 20% of them die of the disease [1]. In China, with the popularity of the hepatitis B virus vaccine, the number of cases of hepatitis B virus infection has been markedly reduced

Table 1. Comparison of general data between the observation group and the control group

General data	Observation group (n = 35)	Control group (n = 45)	*P*
Age (years old)	54.28 ± 9.89	53.36 ± 10.76	0.539
Gender (male/female)	20/15	28/17	0.074
Course of disease (year)	19.26 ± 7.56	17.93 ± 8.03	0.095
BMI (kg/m^2)	23.51 ± 2.42	19.03 ± 2.09	0.032
TC (mmol/L)	5.69 ± 1.01	4.95 ± 1.03	0.378
TG (mmol/L)	1.94 ± 1.03	1.90 ± 0.79	0.073
LDL-C (mmol/L)	3.15 ± 0.91	3.01 ± 0.63	0.426
HDL-C (mmol/L)	1.47 ± 0.49	1.42 ± 0.38	0.508

Table 2. Comparison of the levels of ADPN, FPG, FINS, HOMA-IR, and HbA1c between the observation group and the control group

Relevant index	Observation group (n = 35)	Control group (n = 45)	*P*
FINS (mIU/L)	15.23 ± 3.26	9.79 ± 2.68	0.002
FPG (mmol/L)	9.42 ± 1.05	4.93 ± 0.92	0.001
HbA1c (%)	10.95 ± 1.42	7.29 ± 0.83	0.026
HOMA-IR	8.69 ± 1.35	3.99 ± 1.30	0.029

compared with that before [2], but on the other hand, due to the continuous improvement of living standards and changing lifestyles, the number of people suffering from diabetes mellitus has been gradually on the rise [3]. On the basis of chronic hepatitis B virus infection, the complication with diabetes mellitus will accelerate or exacerbate liver fibrosis, and reduce the antiviral efficacy of patients. Moreover, it is more likely for patients with chronic hepatitis B virus infection complicated with diabetes mellitus to suffer from liver cirrhosis or liver cancer than healthy people or those only with chronic hepatitis B virus infection [4]. At present, pathogenic factors and pathophysiology of chronic hepatitis B complicated with diabetes mellitus are not clear in China and foreign countries, and there are few related studies. Therefore, the relationship between patients with chronic hepatitis B and the complication with diabetes mellitus is worth exploring [5]. The most important site in the body for ingesting, saving, and metabolizing glucose is liver tissue cells that play a very key role in controlling plasma glucose [6]. Necrosis of liver tissue cells caused by chronic hepatitis B virus infection promotes inactivation of insulin resistance, ultimately increasing the reduction of glucose tolerance, and leading to the occurrence of insulin resistance [7]. In chronic hepatitis B patients, correlation of insulin resistance, inflammatory cytokines, and liver cell damage with diabetes mellitus need to be continuously and thoroughly investigated, thus providing significant clinical value in preventing diabetes mellitus.

Materials and methods

General data

A total of 80 patients definitely diagnosed with chronic hepatitis B in our hospital from May 2016 to July 2017 were selected. Among them, 35 patients complicated with diabetes mellitus were included as the observation group, and 45 patients not complicated with diabetes mellitus were included as the control group, including 50 males and 30 females aged 35-78 years old, with an average age of (53.7 ± 16.2) years old. All the selected cases met the diagnostic criteria of the *Guideline on Prevention and Treatment of Chronic Hepatitis B in China (2005)*, and the *Diagnostic Criteria for Type 2 Diabetes Mellitus of the World Health Organization (WHO) (1997)*. Exclusion criteria: 1) patients with a heavy drinking history, with weekly capacity for alcohol of greater than 40 g, 2) patients with liver cirrhosis and liver cancer triggered by serious blood system diseases, malignant tumors, autoimmune diseases, or other causes, 3) patients with serious infections, or 4) patients with incomplete clinical data.

Methods

Clinical data of all patients were retrospectively analyzed, including age, gender, course of chronic hepatitis B, weight and height, and the body mass index (BMI) of them was calculated. The fasting peripheral blood was extracted from all the selected cases after 10 hours of solid and liquid fasting overnight. The upper serum was then taken to measure the levels of biochemical indexes and inflammatory cytokines. Specifically, the levels of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) were determined via immunonephelometry, fasting plasma glucose (FPG) via a glucose oxidase method, hemoglobin A1c (HbA1c) via a glycated hemoglobin analyzer, and fasting serum insulin (FINS), hyaluronic acid (HA), and type III collagen (III-C) and

Table 3. Comparison of liver function indexes between the observation group and the control group (IU/L)

Liver function index	Observation group (n = 35)	Control group (n = 45)	*P*
ALT	93.12 ± 18.56	63.36 ± 17.29	0.001
AST	105.27 ± 13.59	68.77 ± 13.68	0.001
GGT	99.63 ± 10.57	42.82 ± 10.39	0.001

Table 4. Comparison of liver cirrhosis indexes between the observation group and the control group (ng/mL)

Liver cirrhosis index	Observation group (n = 35)	Control group (n = 45)	*P*
HA	6.92 ± 0.58	4.83 ± 0.86	0.001
III-C	3.51 ± 1.73	1.43 ± 1.19	0.001
IV-C	2.99 ± 1.36	0.97 ± 1.42	0.031

Table 5. Comparison of the level of inflammatory cytokines between the observation group and the control group

Inflammatory cytokine	Observation group (n = 35)	Control group (n = 45)	*P*
CRP (mg/L)	6.08 ± 1.39	2.35 ± 0.97	0.001
TNF-α (ng/ml)	12.03 ± 1.16	6.45 ± 1.03	0.001
IL-6 (μg/L)	9.38 ± 1.57	7.03 ± 1.12	0.001

type IV collagen (IV-C) via radioimmunoassay using kits provided by Beijing Keep-Science Analysis Sci&Tech Co., Ltd. Other biochemical indicators [total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), alanine transaminase (ALT), aspartate transaminase (AST) and gamma-glutamyl transferase (GGT)] were measured using an automatic biochemical analyzer provided by Hitachi, Inc. In addition, according to calculation, homeostasis model of assessment for insulin resistance (HOMA-IR) = FINS * FPG/22.5.

Statistical methods

Statistical Product and Service Solutions (SPSS) 19.0 statistical software was adopted for data processing. The collected data are expressed as ($\bar{x} \pm s$). The X^2 test was applied to compare count data. Correlation analysis was conducted for two factors. Relevant risk factors underwent the Logistic analysis. $P < 0.05$ represented that the difference was statistically significant.

Results

Comparison of general data between the observation group and the control group

There were no statistically significant differences in age, gender, course of disease, TC, TG, LDL, and HDL between the observation group and the control group ($P > 0.05$), but the BMI of the observation group was higher than that of the control group ($P < 0.05$) (**Table 1**).

Comparison of the levels of FPG, FINS, HOMA-IR, and HbA1c between the observation group and the control group

The levels of FINS, FPG, HOMA-IR, and HbA1c in the observation group were higher than those in the control group, showing statistically significant differences ($P < 0.05$) (**Table 2**).

Comparison of liver function indexes between the observation group and the control group

Comparisons of liver function indexes between the two groups manifested that the levels of serum ALT, AST, and GGT in the observation group were higher than those in the control group, with statistically significant differences ($P < 0.05$) (**Table 3**).

Comparison of liver cirrhosis indexes between the observation group and the control group

The levels of serum HA, III-C and IV-C in the observation group were higher than those in the control group, and the differences were statistically significant ($P < 0.05$) (**Table 4**).

Comparison of the levels of inflammatory cytokines between the observation group and the control group

The levels of inflammatory cytokines, including CRP, TNF-α, and IL-6, in the observation group were significantly higher than those in the control group, with statistically significant differences ($P < 0.05$) (**Table 5**).

Correlation analyses of insulin resistance index, inflammatory cytokines, liver function indexes, and plasma glucose

Insulin resistance index ($r = 0.757$, $P < 0.001$), ALT ($r = 0.659$, $P < 0.001$) and CRP ($r = 0.603$, $P < 0.001$) were positively correlated with FPG (**Figures 1-3**).

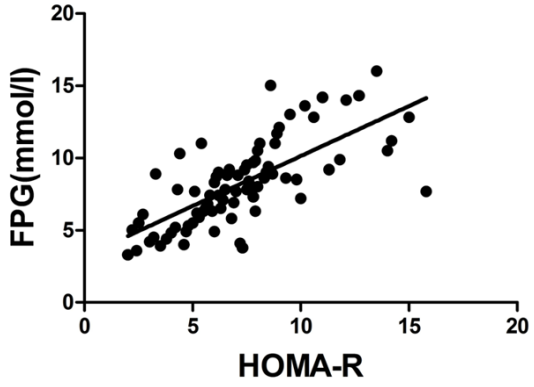

Figure 1. Correlation between HOMA-IR and FPG.

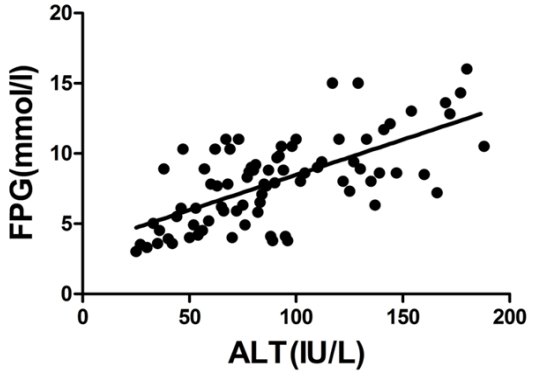

Figure 2. Correlation between ALT and FPG.

Discussion

The complication with diabetes mellitus in patients with chronic hepatitis B virus infection is a double-disease injury [8]. In clinical practice, such patients are not rare. Relevant studies have revealed that patients with chronic hepatitis B virus infection are more prone to developing diabetes mellitus than normal healthy people [9]. This may be related to hepatitis B virus infection, but it is still not very clear [10]. When the body is infected with hepatitis B viruses, liver tissue cells will be damaged to varying degrees of necrosis, thus impeding the removal of insulins and glucagons, and ultimately triggering insulin resistance in the body [11]. Moreover, synthesis of glycogen synthase is reduced due to damage of liver tissue cells, which slows down the metabolism of glucoses in the body and reduces glycogens, so as to increase plasma glucoses [12]. A relevant study has evidenced that insulin resistance index of patients with chronic hepatitis B is significantly higher than that of normal people, and the

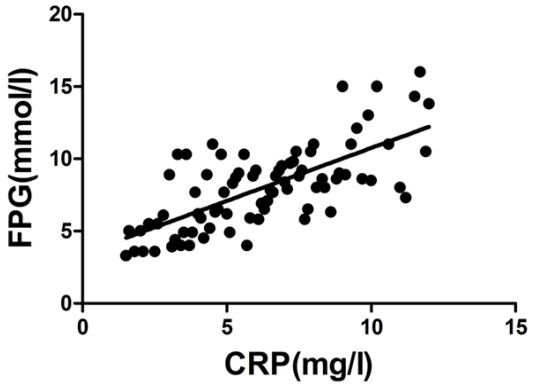

Figure 3. Correlation between CRP and FPG.

increase in insulin resistance index accelerates the progression of liver fibrosis in patients with hepatitis B [13]. Insulin resistance can induce dyslipidemia, vascular endothelial cell damage, increased inflammatory response in the body, as well as hypercoagulability in the blood system [14]. Relevant data have indicated that the probability of developing diabetes mellitus will be increased by about 5% with one-unit increase in insulin resistance index [15]. Approximately 20 years before the onset of diabetes mellitus, insulin resistance occurred, so the probability of developing diabetes mellitus will increase with the prolonged course of chronic hepatitis B [16]. This study demonstrates that the insulin resistance index of chronic hepatitis B patients complicated with diabetes mellitus is significantly higher than that of patients not complicated with diabetes mellitus, and insulin resistance index was positively correlated with fasting glucose, which is consistent with the above conclusions.

Patients with chronic hepatitis B are often accompanied by excessive responses in the inflammatory system as well as excessive synthesis and release of inflammatory cytokines, and the signal transduction within liver tissue cells proceeds based on the mediation by inflammatory cytokines [17]. This process results in phosphorylation of insulin receptor substrates in insulin-sensitive cells, such as liver tissue cells and muscle tissue cells, and it can also lead to insulin resistance due to impaired insulin signal transduction [18]. On the other hand, as inflammatory cytokines, such as TNF-α and interleukin, bind to adipose tissues, causing an imbalance of lipid metabolism, the extracellular free fatty acid content

will be increased, thus triggering insulin resistance [19]. According to relevant studies, when the human body is infected with chronic hepatitis B viruses, the first inflammatory cytokine released by the body is represented by TNF-α. In addition to the phosphorylation of insulin receptor substrates and the increase in inflammatory cytokines, insulin resistance can be also caused by increased glycogen output through degrading lipids and reducing the utilization of glucoses in muscle tissues, thus triggering diabetes mellitus [20]. The study indicates that the levels of serum inflammatory cytokines in chronic hepatitis B patients complicated with diabetes mellitus can be significantly higher than those in patients not complicated with diabetes mellitus, and inflammatory cytokines are positively associated with FPG. Therefore, compared with patients only with chronic hepatitis B infection, patients complicated with diabetes mellitus have more severe insulin resistance and higher levels of inflammatory cytokines, and reducing the levels of circulating inflammatory cytokines is expected to be a new approach to preventing the complication with diabetes mellitus in patients with chronic hepatitis B.

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Disclosure of conflict of interest

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