The Effect of Serum Glucose Levels on Progression of Fibrosis in Patients with Chronic Hepatitis C Infection

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Abstract

Background: Chronic hepatitis C (CHC) infection has a close association with diabetes mellitus. However, Conflicting results exist on the analysis of relationship between serum glucose levels and development of fibrosis. The aim of the present study was to evaluate the impact of serum glucose levels on the longitudinal development of liver fibrosis.

Methods: In this prospective cohort study, a total of 581 CHC patients were followed from September 2012 to September 2014. Advanced liver fibrosis was defined as a The fibrosis-4 index (FIB-4) index score above 3.25. We assessed the prevalence of liver cirrhosis and identified related factors. We also examined the association between hyperglycaemia and longitudinal development of advanced liver fibrosis.

Results: Among 581 patients, 321 (55.2%) showed no advanced fibrosis, 168 (28.9%) showed progression of advanced fibrosis, 81 (13.9%) showed persistent advanced fibrosis and 11 (3.4%) showed improvement at the final visit. Compared to patients with no advanced fibrosis, older age (OR=2.77, 95% CI: 1.85-4.14), heavy alcohol consumption (OR=2.03, 95% CI: 1.22-3.37), and high HCV RNA viral load (OR=3.01, 95% CI: 1.82-4.97) were positively associated with progression of advanced fibrosis. Older age (OR=4.57, 95% CI: 2.58-8.08), hyperglycaemia (OR=3.53, 95% CI: 1.69-7.38), and high HCV RNA viral load (OR=2.44, 95% CI: 1.28-4.65) were independently associated with increased risk of persistently advanced fibrosis.

Conclusions: Hyperglycaemia was not substantially associated with progression of advanced fibrosis in shorter-term, whereas hyperglycaemia was positively associated with persistent advanced fibrosis. Strict control of blood glucose levels should be considered for patients with cirrhosis and diabetes.

Introduction

Hepatitis C virus (HCV) infection is an important global health problem, with an estimated 71 million individuals being infected [1]. In China, the prevalence of HCV is approximately 0.43%, and about 10 million individuals have been estimated to be infected[2]. The natural history of HCV suggests that 55-85% of the infected subjects eventually develop chronic hepatitis C (CHC)[3]. It is s a major cause of cirrhosis, end-stage liver disease (ESLD), and hepatocellular carcinoma (HCC) and is associated with increased mortality[1].

HCV is a systemic disease rather than just a liver disorder. Numerous extrahepatic manifestations have been reported to be related to HCV infection, including mixed cryoglobulinaemia, renal insufficiency, cardiovascular disorders, and diabetes [4, 5]. Several meta-analyses reported that chronic HCV infection significantly increases the risk of to develop type 2 diabetes mellitus (T2DM) [6, 7]. The prevalence rate of diabetes mellitus (DM) in HCV-infected patients ranges from 14.4% to 50%[8]. The underlying mechanism is that HCV promotes peripheral and hepatic insulin resistance and HCV impairs pancreatic β -cell function. Thus, impaired both first-phase and second- phase insulin secretion contributes to HCV-

associated type 2 diabetes [9]. Glucose abnormalities are also associated with advanced liver fibrosis and a higher risk of HCC development[10]. It is associated with increased odds development of fibrosis in the patients with HCV infection [11]. Compared non-diabetes, diabetes patients increased the risk of de novo HCC(HR 2.39, p=0.01)[12]. DM itself seems to have a selective impact on HCC development [13, 14].

The fibrosis-4 index (FIB-4) is a serological test to detect liver fibrosis in patients with chronic hepatitis C infection. It is one of the most widely used non-invasive tools for identifying and staging hepatic fibrosis[15]. An FIB-4 score <1.45 has a negative predictive value of 94.7% to exclude severe fibrosis with a sensitivity of 74.3%. An FIB-4 score higher than 3.25 had a 98.2% specificity and a positive predictive value of 82.1% to confirm the existence of a significant fibrosis (F3-F4)[16]. Currently, FIB-4 index is recommended as a non-invasive pretreatment assessment of liver fibrosis in the Simplified HCV Treatment Algorithm by AASLD, using 3.25 as a cut-off for HCV-related advanced fibrosis or cirrhosis [17].

As reported by previous study, Fuyu city in China has a high prevalence of HCV infection [18]. The majority of patients who live in this area are below the national poverty level. Township hospitals are the prime location for HCV screening and treatment. The application of non-invasive tools such as FIB-4 in evaluating the severity of hepatic fibrosis may have an advantage and potential implications in epidemiological investigation and township hospitals.

Although previous studies confirmed that DM is positive associated with increased risk of HCC[14], little attention has been given to the role of serum glucose levels in fibrosis progression. In this a real-life, prospective cohort study with chronic HCV infected patients, we assessed the prevalence of liver cirrhosis and identified related factors. We also investigated the impact of serum glucose levels on the longitudinal development of advanced liver fibrosis.

Methods

Study population

This was a real-life, prospective cohort study. The study population was derived from 3219 Chinese patients who participated in a retrospective investigation of HCV infection which was performed by the First Hospital of Jilin University in Fuyu City, China in September 2012. The 680 patients with chronic HCV infection were followed up in September 2014. Ninety-nine individuals had missing variables to calculate FIB-4, excluded from analysis. The remaining 581 subjects (341 male and 240 female) constituted the study population.

Ethics statement

This study was approved by the Ethical Committee at the First Hospital of Jilin University (2013-096) and written informed consent was obtained from each subject.

Data collection

In the baseline, each subject had been requested to complete a questionnaire that included information on demographics (eg, age and gender), personal health history (eg, diabetes mellitus) and lifestyle (eg, smoking and alcohol consumption) and then were followed up in two years later. Anthropometric measurements (eg, height and weight) were obtained. Laboratory assessments included liver biochemistry, fasting glucose levels, and virological tests for HCV. Serological markers for anti-HCV and antibody to hepatitis B surface antigen (anti-HBs) were determined by an enzyme-linked immunosorbent assay, using Abbott ARCHITECT i2000SR (Abbott Laboratories, Abbott Park, IL, USA). HCV-RNA testing was performed by the Roche Taqman HCV test (Roche Diagnostics, Grenzach, Germany). Liver biochemistry and fasting blood glucose (FBG) levels and were assessed in the First Hospital of Jilin University according to standard procedures.

Definition

Average alcohol consumption was calculated as the median number of drinks per week during preceding 6-month interval. Heavy alcohol consumption was defined as >1 drink per day or >3 drinks on any day for women and >2 drinks per day or >4 drinks on any day for men [19]. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. High BMI was defined as BMI $\geq$ 25 kg/m². Hyperglycaemia was defined as a fasting blood glucose $\geq$ 100 mg/dL or diagnosis of type 2 diabetes. Hypertriglyceridemia was defined as a triglycerides level $\geq$ 150 mg/dL. Hypercholesterolemia was defined as a total cholesterol level $\geq$ 240 mg/dL. The outcome variable was HCV-related advanced liver fibrosis, defined as a FIB-4 index score of > 3.25. FIB-4 was calculated based on the following formulae: FIB-4 = (Age $\times$ AST) / (platelet count $\times$ $\sqrt{\text{ALT}}$).

Statistical Analysis

Continuous variables were presented as median (interquartile ranges) or mean (SD), and compared by the Mann-Whitney test or two-sample t-test. Categorical variables were expressed as numbers and frequencies (%), and compared by the Pearson Chi-square test or Fisher exact test. Univariate and multivariate logistic regression models were performed to evaluate the association between baseline parameters and advanced liver fibrosis. Variables with *P* values below or equal to 0.10 in univariate analysis were included in the multivariate model. Odds ratio (OR) and 95% confidence intervals (95% CI) were used to determine the strength of statistical associations. A two-sided *P*-value below or equal to 0.05 was considered significant. All statistical analyses were performed using SPSS software package 18.0 (SPSS Inc. USA).

Results

Patient characteristics at baseline

A total of 581 patients were included in this study and 92 (15.8%) patients had advanced fibrosis at baseline. Patients with advanced fibrosis and those without advanced fibrosis were similar in gender, BMI, hypertriglyceridemia and proportion of HBsAg positive. However, the mean age of patients with

advanced fibrosis was higher than those without advanced fibrosis (58.8 versus 53.6 years, $P < 0.001$). Patients with advanced fibrosis had significantly higher prevalence of high HCV RNA level (87.0% versus 72.4%, $P = 0.003$). Patients with advanced fibrosis were more likely to have hyperglycaemia (29.3% versus 14.1%, $P < 0.001$) and less likely to have hypercholesterolemia (1.1% versus 7.4%, $P = 0.024$). Features of the study populations and differences in the variables potentially associated with advanced fibrosis are shown in Table 1.

Univariate and multivariate analysis of variables associated with advanced fibrosis

The results of univariate and multivariate analysis are provided in Table 2. According to univariate analysis, older age (OR=3.17, 95% CI: 1.94-5.19), high HCV RNA viral load (OR=2.54, 95% CI: 1.34-4.81), and hyperglycaemia (OR=2.53, 95% CI: 1.51-4.24) were associated with an increased probability of advanced fibrosis. After adjusting for potential confounders, older age (OR=2.99, 95% CI: 1.80-4.95), high HCV RNA viral load (OR=2.25, 95% CI: 1.17-4.33), and hyperglycaemia (OR=2.33, 95% CI: 1.36-4.00) were the only three variables independently associated with advanced liver fibrosis on multivariate analysis. Patients with hyperglycaemia compared to those without hyperglycaemia had a 2.33-fold increased rate of advanced fibrosis.

Baseline factors associated with longitudinal progression of fibrosis

We analyzed the longitudinal progression of fibrosis in 581 CHC patients who underwent 2 assessments of FIB-4. Compared with baseline, the median value of FIB-4 score was significantly higher at two-year follow up visit (2.91 versus 1.84, $P < 0.001$). At two-year follow-up, 55.2% (321 of 581) of patients had no advanced fibrosis ($\text{FIB-4} \leq 3.25$) and 3.4% (11 of 581) of patients had improvement of fibrosis (defined as FIB-4 reversion to ≤ 3.25). However, 28.9% (168 of 581) of patients experienced progression of fibrosis (defined as FIB-4 elevation to > 3.25) and 13.9% (81 of 581) of patients presented persistent advanced fibrosis (defined as $\text{FIB-4} > 3.25$ at both two visits). Baseline factors associated with longitudinal FIB-4 patterns were shown in Table 3. In multivariable analysis, older age (OR=2.77, 95% CI: 1.85-4.14), heavy alcohol consumption (OR=2.03, 95% CI: 1.22-3.37), and high HCV RNA viral load (OR=3.01, 95% CI: 1.82-4.97) were positively associated with progression of advanced fibrosis. Older age (OR=4.57, 95% CI: 2.58-8.08), hyperglycaemia (OR=3.53, 95% CI: 1.69-7.38), and high HCV RNA viral load (OR=2.44, 95% CI: 1.28-4.65) were independently associated with increased risk of persistent advanced fibrosis. As shown in Table 4.

The impact of longitudinal changes of serum glucose levels on advanced fibrosis

During a two-year follow-up, 78% (453 of 581) patients showed persistent normal fasting blood glucose, defined as FBG < 100 mg/dL both at baseline and two-years follow-up visit. 22.0% (128 of 581) patients had intermittent/persistent fasting blood glucose elevation, defined as $\text{FBG} \geq 100$ mg/dL at one or two visits. At two-year follow up visit, the median value of FIB-4 score in patients with intermittent or persistent FBG elevation was higher than that in patients with persistent normal FBG (2.85 versus 3.23, $P = 0.031$), as shown in Fig 1. A significant higher prevalence of intermittent/persistent fasting blood

glucose elevation was observed in patients with persistent FIB-4 > 3.25 than in patients with persistent normal FIB-4 (Fig 2).

Discussion

In this prospective cohort study of patients infected with HCV, 15.8% patients had advanced fibrosis at baseline. After two-year follow up, 13.9% of patients presented persistent advanced fibrosis and 28.9% of patients experienced progression of fibrosis. Older age, hyperglycaemia, and high HCV RNA viral load were independently associated with increased risk of current and persistent advanced fibrosis. Older age, heavy alcohol consumption, and high HCV RNA viral load were positively associated with progression of advanced fibrosis.

The results of present study showed that hyperglycaemia was positively associated with advanced fibrosis. It was consistent with previous reports [20-24]. Previous study also shows that insulin resistance is significant associated with liver fibrosis [22, 25]. Our study confirmed hyperglycaemia was a significant predictor of advanced fibrosis in Chinese patients. Plausible mechanisms exist to explain the role of high serum glucose in hepatic fibrogenesis. Liver fibrosis progression is promoted by activated hepatic stellate cells (HSCs). Hyperglycemia enhanced formation and deposition of advanced glycation products that activate hepatic stellate cells [22, 26]. High glucose could directly stimulate hepatic stellate cells to proliferate and to produce type I collagen production [27]. Further, high glucose concentrations cause up-regulation of connective tissue growth factor and other profibrogenic cytokines [28]. Alfaleh *et al*/reported that diabetes mellitus was also an independent predictor of disease progression in patients with chronic hepatitis C genotype 4 after interferon-based therapy [29]. However, we found no significantly association between high glucose and progression of advanced fibrosis. It was verified by Rueger *et al*/who found diabetes failed to contribute to accelerated fibrosis progression rate [30]. Fewer studies focused on the effect of high glucose on progression of fibrosis. The main reason for these differences may be the endpoints were various. The endpoint was development of the hepatic decompensation or HCC, liver transplantation or liver-disease-related mortality in the study of Alfaleh. It was the long-term outcome of chronic HCV infection. However, the endpoint was short-term progression of fibrosis in this study. Metabolic and hepatic disorders become apparent only after years of follow up. In this study, the follow-up period was only two years. It might be too short to confirm possible association. But we found that the FIB-4 score in patients with intermittent or persistent FBG elevation was higher than that in patients with persistent normal FBG at final visit. It confirmed that high serum glucose had effect on progression of fibrosis. In HCV-related cirrhosis patients, the status of glycemic control was a significant independent factor of survival [31]. Therefore, strict control of blood glucose levels should be considered for patients with cirrhosis and DM.

Our study confirmed that heavy alcohol consumption was significantly associated with progression of advanced fibrosis. It was consistent with previous study [32]. Kelly *et al*/reported that very heavy drinking showed significant fibrosis acceleration compared to abstaining in HIV/HCV-coinfected women [33]. CHC patients with excessive alcohol consumption had even higher risks for overall mortality and liver related

mortality [34]. The patients with chronic HCV infection should be counseled to minimized alcohol drinking. In addition to alcohol, fibrosis progression was also associated with older age and high HCV viral load. Older age is consistently related to greater progression of HCV-related liver disease [21, 35, 36]. Several previous study reported that an association between fibrosis progression and age at infection, with a higher rate of fibrosis progression in patients with an older age at infection [37]. Based on progression rates, most HCV patients are expected to develop cirrhosis at about 65 years old without regard to age at infection. Thus, age itself seems even more important than age at infection for predicting the occurrence of liver cirrhosis[38]. In this study, we confirmed that older age was an independent predictor of existed advanced fibrosis and progression of advanced fibrosis. It is important to highlight the need for cirrhosis screening and follow-up in older patients with CHC infection. High HCV viral loads may be associated with fibrosis progression, as demonstrated in the majority of studies[39]. HCV eradication is associated with lower rates of liver fibrosis progression. It could halts progression to liver cirrhosis and hepatocellular carcinoma[40]. Antiviral therapy is an essential treatment for patients with chronic HCV infection. It is recommended for all adults CHC patients with the advent of direct-acting antiviral regimens[41].

Conclusion

High serum glucose had effect on progression of fibrosis. Hyperglycaemia was related to increased risk of current and persistent advanced liver fibrosis. However, no significantly association existed between high glucose and progression of advanced fibrosis in short-term follow-up. Strict control of blood glucose levels should be considered for patients with cirrhosis and DM.

Abbreviations

CHC: chronic hepatitis C; FIB-4: fibrosis-4 index; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; ESLD: end-stage liver disease; DM: diabetes mellitus; T2DM: type 2 diabetes mellitus; anti-HBs: hepatitis B surface antigen; FBG: fasting blood glucose; HSCs: hepatic stellate cells; BMI: body mass index.

Declarations

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Authors' contributions

Qinglong Jin and Yawen Liu designed and conducted most of the study; Fei Kong wrote the first draft of the manuscript; Xiumei Chi, Ruihong Wu and Xiaomei Wang performed biochemical testing; Fei Kong, Yu Pan, Juan Lv, Haibo Sun, Ge Yu, Yang Wang, XiuZhu Gao, Mingyuan Zhang and Jing Jia collected the epidemiological and clinical data; Fei Kong and Hongqin Xu performed the statistical analyses; Junqi Niu, Yawen Liu and Qinglong Jin reviewed and corrected manuscript.

Availability of data and materials

The data is available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethical Committee at the First Hospital of Jilin University (2013-096) and written informed consent was obtained from each subject.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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Tables

Table 1. Baseline characters of study population

Characteristic	No advanced fibrosis (n=489)	Advanced fibrosis (n=92)	<i>P</i> value
Age (ys, SD)	53.6 (7.5)	58.8 (7.9)	<0.001
Gender (%)			
Male	281 (57.5)	60 (65.2)	0.166
Female	208 (42.5)	32 (34.8)	
Smoking history (%)			0.704
No	191 (39.1)	34(37.0)	
Yes	298(60.9)	58(63.0)	
Heavy alcohol consumption (%)			
No	364 (74.4)	62 (67.4)	0.161
Yes	125 (25.6)	30 (32.6)	
HBV co-infection (%)			
No	453(92.6)	87(94.6)	0.508
Yes	36 (7.4)	5 (5.4)	
HCV RNA(%)			
≤1000IU/ml	135(27.6)	13(13.0)	0.003
>1000IU/m	354(72.4)	87(87.0)	
hyperglycaemia (%)			
No	420 (85.9)	64(70.7)	<0.001
Yes	69(14.1)	27(29.3)	
BMI ≥ 25kg/m ² (%)			
No	310(63.4)	62(67.4)	0.464
Yes	179(36.6)	30(32.6)	
Hypertriglyceridemia (%)			
No	315(64.4)	61(66.3)	0.728
Yes	174(35.6)	31(33.7)	
Hypercholesterolemia(%)			
No	453(92.6)	91(98.9)	0.024

Yes

36(7.4)

1(1.1)

Table 2. Univariate and multivariate analysis of factors associated with advanced liver fibrosis

Characteristic	Univariate analysis (n=581)		Multivariate analysis (n=581)	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Age				
≤55 ys	Reference	<0.001	Reference	<0.001
>55 ys	3.17(1.94-5.19)		2.99(1.80-4.95)	
Gender		0.167		0.188
Male	Reference		Reference	
Female	0.72(0.45-1.15)		0.72(0.44-1.17)	
HCV RNA		0.004		0.016
≤1000IU/ml	Reference		Reference	
>1000IU/ml	2.54(1.34-4.81)		2.25(1.17-4.33)	
Hyperglycaemia				
No	Reference	<0.001	Reference	0.002
Yes	2.53(1.51-4.24)		2.33(1.36-4.00)	
Hypercholesterolemia				
No	Reference	0.052	Reference	0.058
Yes	0.14(0.02-1.02)		0.14(0.02-1.07)	

Table 3 Baseline characters and longitudinal FIB-4 patterns

Characteristic	Persistent FIB-4 ≤3.25 (n=321)	FIB-4 elevation to>3.25 (n=168)	Persistent FIB >3.25 (n=81)	<i>P</i> value
Age (ys, SD)	52.3 (7.5)	56.1 (7.0)	59.1 (8.1)	<0.001
Sex (%)				
Male	176 (54.8)	105 (62.5)	54 (66.7)	0.160
Female	145(45.2)	63 (37.5)	27 (33.1)	
Smoking history (%)				
No	126 (39.3)	65 (38.7)	30(37.0)	0.986
Yes	195(60.7)	103 (61.3)	51(63.0)	
Heavy Alcohol use (%)				
No	252 (78.5)	112 (66.7)	56 (69.1)	0.012
Yes	69(21.5)	56 (36.1)	25(30.9)	
HBV co-infection (%)				
No	297(92.5)	156 (92.9)	76(93.8)	0.825
Yes	24 (7.5)	12(7.1)	5(6.2)	
HCV RNA (%)				
≤1000IU/ml	110(34.3)	25(14.9)	10(12.3)	<0.001
>1000IU/ml	211(65.7)	143(85.1)	71(87.7)	
Anti-viral treatment (%)				
No	244(76.0)	123(73.2)	67(82.7)	0.416
Yes	77(24.0)	45(26.8)	14(17.3)	
BMI ≥ 25kg/m ² (%)				
No	196(61.1)	114 (67.9)	55(67.9)	0.425
Yes	125(38.9)	54(32.1)	26(32.1)	
Hyperglycaemia (%)				
No	276(86.0)	144(85.7)	58(71.6)	0.005
Yes	45(14.0)	24(14.3)	23(28.4)	
Hypertriglyceridemia (%)				

No	206(64.2)	109(64.9)	55(67.9)	0.815
Yes	115(35.8)	59(35.1)	26(32.1)	
Hypercholesterolemia (%)				
No	194(91.6)	159(94.6)	80(98.8)	0.076
Yes	27(8.4)	9(5.4)	1(1.2)	

Table 4 Association between baseline characters and longitudinal fibrosis progression in multivariate analysis

Characteristic	Progression of advanced fibrosis (n=479)		Persistent advanced fibrosis (n=402)	
	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Age				
≤55	Reference	<0.001	Reference	<0.001
>55	2.77(1.85-4.14)		4.57(2.58-8.08)	
Sex		0.993	0.329	
Male	Reference		Reference	
Female	0.99(0.63-1.59)		0.73(0.39-1.37)	
Heavy Alcohol consumption		0.006	0.220	
No	Reference		Reference	
Yes	2.03(1.22-3.37)		1.52(0.78-2.99)	
HCV RNA				
≤1000IU/ml	Reference	<0.001	Reference	0.001
>1000IU/m	3.01(1.82-4.97)		3.53(1.69-7.38)	
hyperglycaemia				
No	Reference	0.823	Reference	0.007
Yes	1.06(0.60-1.89)		2.44(1.28-4.65)	
Hypercholesterolemia				
No	Reference	0.291	Reference	0.055
Yes	0.64(0.28-1.46)		0.13(0.02-1.05)	

Figures

Figure 1

Distribution of FIB-4 score in patients with persistent normal FBG and intermittent or persistent FBG elevation

Figure 2

The impact of longitudinal changes of fasting blood glucose on advanced fibrosis