Approximately 185 million people are infected with hepatitis C virus (HCV) worldwide and up to 84% of patients with acute HCV infection develop chronic infection. Although protease inhibitors and other newly developed anti-viral drugs have been used in the West, pegylated interferon (Peg-IFN) -α and ribavirin (RBV) combination therapy for chronic hepatitis C (CHC) is still the standard treatment for HCV infection in China.¹,² Clinically, 21-50% of CHC patients have diabetes mellitus, suggesting an association with diabetes. Further analysis indicates that patients with cirrhosis induced by chronic HCV infection are more prone to diabetes compared to CHC patients.³ Whether Peg-IFN-α and RBV combination therapy is associated with development of diabetes and has effects on glucose metabolism is unknown.

Chronic HCV infection causes several liver-related diseases, including cirrhosis, liver failure, and hepatocellular cancer after years or decades. Effective treatment of early-stage cirrhosis can block the development of liver failure and hepatocellular cancer due to chronic HCV infection. Progression to cirrhosis is often clinically si-
lent and liver biopsy is the gold standard diagnostic test for cirrhosis. However, a liver biopsy test is not efficient for liver cirrhosis diagnosis because fibrosis is not usually uniform throughout the liver. The FibroScan, as an emerging technique, is widely used to quantify hepatic fibrosis in a non-invasive and painless manner that is accurate and repeatable. Thus, we used FibroScan to monitor the outcome of Peg-IFN-α and RBV combination therapy for cirrhosis.

PATIENTS AND METHODS

Study population
Chronic HCV genotype 1-infected patients who visited 302 Military Hospital of China from October 2011 through September 2012 were enrolled in the study. The diagnostic criteria were based on 2011 European HCV clinical practice guidelines issued by the European Association for the Study of the Liver. Patients with other hepatitis viruses or human immunodeficiency virus co-infection, or other chronic liver conditions (hemochromatosis, autoimmune hepatitis, drug-induced hepatitis, alcoholic liver diseases, and others) were excluded. The study was approved by the ethics committee of 302 Military Hospital of China, and carried out in compliance with the Helsinki declaration. All patients gave written informed consent. All patients received standard anti-HCV treatment with Peg-IFN-α (180 µg once per week) or Peg-IFN-α (1.5 µg/kg once per week) plus RBV (15 mg/kg per day). (PegIntron, Merck Sharp & Dohme Italia SPA, Via Emilia 21 PAVIA 27100, Italy).

Liver stiffness measurements
Liver stiffness was measured with a FibroScan (Echosens, Paris, France) system based on transient elastography. The right lobe of the liver was accessed through the intercostal space while the patient lay on their right arm at maximal abduction. A probe covered with coupling gel was placed on the skin. The result was reliable only when 10 successful shots with more than a 65% success rate were obtained. All the FibroScan detections were carried out by the same operator.

Clinical parameters
Biochemical and serological markers and HCV RNA levels are routinely detected in the Central Clinical Laboratory of Beijing 302 Hospital. The lower limit of detection for HCV RNA is 15 IU/mL (COBAS, Roche). All the patients were evaluated at baseline, 12, 24, 48 weeks during treatment and 24, 48 weeks after end of treatment. The clinical parameters included age, sex, body weight, HCV genotype, liver stiffness (kPa), HCV RNA, alanine aminotransferase (ALT), fasting blood glucose (FBG), 2-hour postprandial blood glucose (PG2-2h), glycosylated hemoglobin (HbA1c), total cholesterol (TC), and triglyceride (TG).

Statistical analysis
Normally distributed data are presented as mean and standard deviation. Statistical comparisons were done by the t test. Data with asymmetric distributions are presented as median (quartiles) and analyzed by a nonparametric test. Correlation was analyzed by the Spearman correlation method. A P value (two-tailed) of <.05 was considered statistically significant. All statistical analyses were carried out with Statistical Program for Social Sciences (SPSS 18.0 for Windows; SPSS Inc., Chicago, IL, USA).
RESULTS

Patient characteristics
Of 116 patients enrolled, all achieved early virological response (EVR), defined as the absence of detectable HCV RNA at week 12 of treatment. HCV RNA remained negative until week 48 of treatment. About three quarters (77.6%; 90/116) of patients achieved sustained virologic response 24 weeks after the end of treatment (SVR), while 26 did not. Baseline demographic and clinical characteristics of the study patients according to virologic response are shown in Table 1.

Improvement of liver inflammation and fibrosis after antiviral therapy
Liver inflammation reduction and fibrosis improvement are showed in Figure 1. In both SVR and non-SVR patients, FibroScan values decreased from 11.3 kPa at baseline to 5.0 kPa at week 72 after EOT in SVR patients, and from 10.2 kPa to 6.2 kPa in non-SVR patients (P<.01). ALT decreased from 88.7 ± 88.4 U/L to 26.5 ± 11.5 U/L in SVR cases, and from 62.4 ± 45.6 U/L to 19.0 ± 4.8 U/L in non-SVR cases, respectively.

Improvement of glucose and lipid metabolism after antiviral therapy
After PR48 treatment, all parameters associated with glucose and lipid metabolism decreased significantly from baseline by 24-weeks (P<.05 from baseline for all SVR comparisons at 24 weeks) (Figure 2). Decreases in TG and TC were significant 48 weeks after the end of treatment. In non-SVR patients, glucose metabolism improved during the 48-week treatment, but at the end of treatment, there was no significant improvement. Paired t-test analysis showed that there were no changes in lipid metabolism in non-SVR patients during the entire period of treatment compared with baseline.

DISCUSSION
HCV causes chronic hepatitis, which can progress to cirrhosis and hepatocellular carcinoma. Furthermore, HCV appears to interact with some aspects of glucose and lipid metabolism. Antiviral therapy with Peg-IFN-α plus RBV is the leading treatment for relief of liver inflammation and regression of fibrosis in China. In the present study, we tried to clarify the impact of effective antiviral treatment on the glucose and lipid metabolism. Firstly, we focused on the antiviral treatment effectiveness. Clinically, sustained virologic response and an absence of HCV RNA by polymerase chain reaction six months after stopping treatment, is an indicator of successful anti-viral treatment. We used ALT, HCV RNA and FibroScan to assess the effectiveness of antiviral treatment. For evaluation of liver histology, liver biopsy (LB) is still the gold standard, but is not accepted well by either patients or physicians because of its invasive and potentially life-threatening. Also, the accuracy of LB is only 65% for a diagnosis of liver cirrhosis because uniformity of fibrosis throughout the liver is rare. Moreover, a static liver biopsy may not reflect the dynamic of fibrosis and the repair of liver injury. An alternative non-invasive method for the diagnosis of fibrosis is FibroScan. FibroScan is based on an ultrasound technique that measures the velocity of propagation of elastic waves through the liver, which is a promising alternative for LB because of its main advantage simplicity, and the possibility of more frequent assessments. In our study, all of the 116 patients achieved EVR, 77.6% (90/116) achieved SVR, while 22.4% (26/116) did not achieve SVR. However, after treatment, liver stiffness measured by FibroScan was significantly reduced whether or not SVR was achieved. Median FibroScan values changed by -55.8% (patients with SVR), and -41.2% (patients without SVR), which represents an improvement in liver histology. In addition, most cirrhotic patients (FibroScan ≥ 18.0 kPa before treatment) had low FibroScan values at the end of follow-up. We can conclude that a significant improvement in liver fibrosis can be achieved with Peg-
IFN-α plus RBV combination therapy in HCV GT1b patients, which is, most importantly, independent of virologic response.

Secondly, we tried to figure out the impact of antiviral treatment on glucose and lipid metabolism. Since HCV was identified in the late 1980s, chronic HCV infection has been verified as a complex multifaceted disease with manifestations extending beyond the liver. It has been well documented that HCV infection correlates strongly with glucose metabolism disorder, which is caused by insulin resistance (IR) and the damage of insulin secretion. IR occurs either because of down-regulation of insulin receptor or the cells are unable to use insulin effectively. Clinical studies have suggested that HCV is a risk factor for the development of glucose metabolism disorder and have shown that CHC patients were more prone to diabetes compared with healthy people or non-HCV-induced hepatitis patients, such as chronic HBV patients. Additionally, many studies have demonstrated that hepatic steatosis (along with bile duct injury and portal lymphoid aggregates) is a prominent feature of HCV. The overall prevalence of steatosis in CHC patients was 55.54%, which was two- to three-fold higher than that in other chronic liver diseases due to HBV, autoimmunity and drugs, and other causes. Interestingly, the majority of CHC patients had mild (<30% of the hepatocytes) steatosis. In our study, glucose and lipid metabolism were improved with effective antiviral therapy in SVR patients (P<.05), which indicated that effective antiviral therapy improved glucose homeostasis. On the other hand, during the follow-up of non-SVR patients, there was no obvious decline in glucose, suggesting that glucose metabolism disorder could impair the SVR to antiviral therapy. Moreover, no lipid changes in non-SVR patients during the duration of PR48 therapy indicated that lipid changes might be a predictor of SVR to PR48 treatment, and should be studied further.

Furthermore, there are several limitations to our study. Firstly, we did not calculate the homeostasis model assessment for insulin resistance index (HOMA-IR), which is a measure of insulin resistance, because by the end of the study, we could not detect fasting insulin at our hospital. Secondly, we did not observe other variables that can lead to improvement of glucose and lipid metabolism, such as diet, sport, and changing lifestyle. Finally, there was no data for other newer regimens to treat CHC patients, such as direct-acting antivirals (DAAs) because they have not been not approved in China. Also, there was only one ethnic group and one treatment center, and a multicenter study should be conducted.

Taken together, the dynamic of liver fibrosis was successfully monitored by FibroScan during the treatment of CHC patients infected with GT1b HCV. A
significant improvement in liver fibrosis can be achieved with antiviral therapy in GT1b patients regardless of virologic response. In addition, effective antiviral therapy can improve glucose and lipid homeostasis, which reduces the burden of metabolic disorders. PR48 therapy is still the primary treatment in Chinese patients with GT1b HCV infection.

**Conflict of interest**

None.

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