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• VIRAL HEPATITIS •

Glucose intolerance in Chinese patients with chronic hepatitis C

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Abstract

AIM: To investigate the prevalence and the risk factors of glucose intolerance in Chinese patients with chronic hepatitis C and to evaluate the relationship between interferon (IFN) treatment and glucose intolerance in these patients.

METHODS: Prospective cross-sectional study was done to evaluate the prevalence of glucose intolerance in Chinese patients with chronic hepatitis C virus (HCV) infection from the outpatient clinic of Department of Family Medicine, Taipei Veterans General Hospital. Chronic hepatitis C was defined as persistent presence of anti-HCV and persistent elevation of liver transaminase for at least 1.5 folds for at least 6 months. Moreover, patients were further categorized into normal fasting glucose and glucose intolerance (diabetes mellitus (DM) and impaired fasting glucose) according to the diagnostic criteria of American Diabetic Association.

RESULTS: Totally, 359 Chinese patients with chronic hepatitis C were enrolled (212 males and 147 females, mean age=58.1±13.0 years). One hundred and twenty-three patients (34.3 %) had received various forms of IFN treatment. One hundred and twenty-five patients (34.6 %) had glucose intolerance, including 99 patients (27.6 %) with DM and 26 patients (7.0 %) with impaired fasting glucose. In comparison with those with normal fasting glucose levels, patients with chronic hepatitis C with glucose intolerance were significantly older, had a significantly higher body mass index, and they were more likely to suffer from obesity, to have family history of diabetes and to have had previous IFN treatment. Stepwise multivariate logistic regression revealed significantly that age ≥57 years, obesity, previous history of IFN treatment and the presence of family history of diabetes were independent risk factors associated with the presence of glucose intolerance in chronic hepatitis C patients.

CONCLUSION: In conclusion, 34.6 % of Chinese patients with chronic hepatitis C had glucose intolerance. Chronic hepatitis C patients who were older in age, obese, had previous IFN treatment history and had family history of diabetes were prone to develop glucose intolerance. To our knowledge, this is the first population-based report to confirm that interferon treatment to be an independent risk factor to develop glucose intolerance.

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INTRODUCTION

Hepatitis C virus (HCV) infection has become a common worldwide medical problem. Patients with chronic HCV infection may develop various extrahepatic manifestations including cryoglobulinemia, the presence of serum autoantibodies, glomerulonephritis, sialoadenitis and porphyria cutaneous tarda[1-3]. The association of chronic HCV infection and diabetes mellitus (DM) was first reported by Alison *et al*. in 1994[4]. Based on case-control studies, the prevalence of DM had been reported in 21 % to 50 % of patients with chronic HCV infection, which was significantly higher than that in the general population or among patients with other diseases[4-7]. Population surveys from western countries also demonstrated that chronic HCV infection was associated with a high incidence of DM[5,7]. In addition, the prevalence of anti-HCV was significantly higher in patients with DM than in the general population[8,9].

The cause of a higher prevalence of DM in patients with chronic HCV infection remains unclear. Altered glucose metabolism has been well documented in patients with chronic liver diseases, especially in patients with liver cirrhosis[10]. However, patients with HCV-related liver cirrhosis is associated with a significantly higher prevalence of DM than those cirrhotic patients with other etiologies[1]. Furthermore, recipients of HCV-related liver transplantation were more likely to develop post-transplantation DM when compared to recipients with other etiologies[6,11]. Therefore, HCV infection *per se* plays an important role in the pathogenesis of DM in patients with chronic HCV infection. Yet, analysis in previous studies rarely considered the confounding factors associated with DM development such as age, obesity and diabetic family history.

Interferon (IFN) has been widely used in the treatment of patients with chronic hepatitis C[12-16]. Development of DM has also been reported as an adverse effect of IFN-α treatment in patients with chronic hepatitis C[17,18]. In addition, exacerbation of previous diabetic control has been reported in chronic hepatitis B patients who received IFN-α treatment[19]. The mechanism of IFN-related DM development or exacerbation of glycemic control remains unclear.

According to the American Diabetic Association (ADA) criteria, DM is diagnosed as repeated fasting plasma glucose ≥126 mg/dL, and impaired fasting glucose (IFG) is defined as the fasting plasma glucose >110 mg/dL and <126 mg/dL[20]. Patients with IFG were reported to be prone to develop DM[21]. Previous studies focused on the relationship of chronic HCV infection and DM. Patients with IFG were rarely evaluated. The purpose of this study was to evaluate the prevalence of

glucose intolerance (DM and IFG) in Chinese patients with chronic hepatitis C in Taiwan. In addition, risk factors associated with DM development such as age, body mass index (BMI), diabetic family history in first-degree relatives and previous IFN treatment were also evaluated to clarify the possible role of chronic HCV infection in association with the development of DM.

MATERIALS AND METHODS

Demographic data

From July 1999 to June 2001, we conducted a cross-sectional study by enrolling and following patients who were previously or newly diagnosed as chronic hepatitis C in the Office Clinics of Taipei Veterans General Hospital in Taipei, Taiwan. The diagnosis of chronic hepatitis C was based on the presence of serum anti-HCV with or without histological confirmation. At least twice for more than 6 months, all patients had elevated serum alanine aminotransferase levels 1.5-fold above the upper limit of the normal value (>60 U/L). Patients who had positive serum hepatitis B surface antigens and chronic liver diseases were excluded.

According to the ADA diagnostic criterias, diagnosis of DM was established according to the documentation of DM in previous medical records and/or repeated fasting plasma glucose ‴℞ mmol/L (126 mg/dL), and IFG was diagnosed with a FPG >110 mg/dL and <126 mg/dL[20]. In this study, both patients with DM and IFG were categorized together as having glucose intolerance to compare them with patients with normal glucose tolerance.

The BMI and family history of DM were recorded for each patient during enrollment. The BMI was expressed as the body weight (in kilograms) divided by the square of the body length (in meter). The family history of diabetes was obtained from the patients themselves and was recorded as positive if their first-degree relatives had DM. Obesity was defined when BMI was >27 Kg/m^2 in males and >25 Kg/m^2 in females[22]. Liver cirrhosis was diagnosed by either liver histology or by characteristic findings in abdominal sonography, computed tomography, celiac angiography and/or the presence of esophageal varices and ascites.

IFN treatment

We recorded details of patients who received IFN treatment, including various regimens of IFNα-2a, IFNα-2b, consensus IFN, subcutaneous injections three times a week, and long-acting pegylated IFNα-2a subcutaneous injections once a week with or without oral ribavirin for either 24 weeks or 48 weeks[23-26].

Biochemical data

Series of biochemical tests including serum alanine aminotransferase and fasting plasma glucose were measured by using an autoanalyzer (Hitachi sequential multiple autoanalyzer; Model 736, Tokyo, Japan). Antibodies to HCV were measured by using a second-generation enzyme immunoassay containing both structural and non-structural antigens (EverNew, Taipei, Taiwan). Hepatitis B surface antigens were measured by using a radioimmunoassay (Abbott Laboratories, Chicago, IL, USA).

Statistical analysis

Data in the text and tables are expressed as mean ± standard deviation (mean ± S.D.). Results were compared between groups depending on the type of data analyzed using the Chi-squared test, Student *t*-test or Mann-Whitney *U*-test. Stepwise multivariate logistic regression (SPSS 10.0, Chicago, IL, USA) was performed to evaluate the predictive variables associated with the presence of glucose intolerance in patients with chronic hepatitis C. For all tests, results with *P* values less than 0.05 were considered statistically significant.

RESULTS

General data of patients

Totally, 359 patients (212 males and 147 females) were enrolled in this study and completed their follow-up investigations in the Office Clinic for more than six months. The mean age of all patients was 58.1±13.0 years old (ranging from 22 to 85 years old). Among these patients, 112 (31.2 %) had a previous history of blood transfusion. Patients without a transfusion history had a past history of undisposable needle injections. None of these patients were intravenous drug abusers or under regular hemodialysis. Among all patients, 66 (18.4 %) of them had a family history of diabetes. The mean BMI of all patients was 24.0±3.5 Kg/m^2. Eighty-seven (24.2 %) patients were obese. One hundred and fifty patients had received a percutaneous liver biopsy. Clinical and histology-diagnosed liver cirrhosis was identified in 75 patients (20.9 %). One hundred and twenty-three patients (34.3 %) had a prior history of IFN treatment with a mean duration of 3.3 years (ranging from 0.5 to 7 years) from completion of IFN treatment till enrollment.

Results of glucose intolerance

Among the 359 patients, 125 patients (34.6 %) had glucose intolerance, including 99 patients (27.6 %) with DM, and 26 patients (7.0 %) with IFG. The remaining 234 patients had normal fasting glucose. None of the 125 patients with glucose intolerance were diagnosed as type 1 DM. The mean age of chronic hepatitis C patients with glucose intolerance was significantly older than the age of those with normal fasting glucose (61.1±11.2 *vs* 56.6±13.6 years; *P*=0.001). The mean BMI of chronic hepatitis C patients with glucose intolerance was significantly higher than that of those with normal fasting glucose (24.5±3.7 *vs* 23.7±3.2 Kg/m^2, *P*=0.024). Thirty-eight of the 125 (30.4 %) patients with glucose intolerance were obese, which was significantly higher than those with normal fasting glucose (53/235, 22.6 %, *P*=0.02). Chronic hepatitis C patients with glucose intolerance had a significantly higher rate of diabetic family history than those with normal fasting glucose (29.6 % *vs* 12.8 %, *P*<0.001, Table 1).

Table 1 Comparisons of demographic data between chronic hepatitis C patients with glucose intolerance* and normal fasting glucose

	Patients with glucose intolerance (*n*=125)	Patients with normal fasting glucose (*n*=234)	*P* value
Age	61.1±11.2	56.6±13.6	0.001
Sex (male:female)	47:78	99:135	0.452
Body mass index (Kg / m^2)	24.5±3.7	23.7±3.2	0.024
Family history of DM (+:-)	37:88	30:204	<0.001
Obesity (+:-)	38:87	49:185	0.046
Liver cirrhosis (+:-)	28:97	47:187	0.706
Previous interferon treatment (+:-)	51:74	66:168	0.021

Denotes: Data were expressed as mean±S.D. * Patients with glucose intolerance included patients with diabetes mellitus and impaired fasting glucose by the diagnostic criteria of the American Diabetic Association.

Data of IFN treatment

One hundred and seventeen patients (32.6 %) had a previous history of IFN treatment. Among these 117 patients, 44 patients were treated with consensus IFN 3 μg (*n*=14), 9 μg (*n*=17) or 15 μg (*n*=13) for 24 weeks, 29 patients were treated with IFNα-2b 3 million units (MU) three times a week for 24 weeks, 4 patients were treated with IFNα-2a 6 MU three times a week for 12 weeks followed by 3 MU three times a week for 36 weeks, and 7 patients were treated with IFNα-2b 3 MU three times a week for 48 weeks along with oral ribavirin (1 000 mg/day for patients who weighed less than 75 Kg, and 1 200 mg/day for those who weighed more than 75 Kg).

Twenty-seven patients were treated with pegylated IFNα-2a 180 μg once a week for 48 weeks, and 19 of them also received oral ribavirin treatment. Six patients received pegylated IFNα-2a 180 μg once a week and oral ribavirin for 24 weeks. In patients who had a previous history of IFN treatment, 42.7 % (50/117) were glucose intolerant, which was significantly higher than the 30.2 % (73/242) of those without a history of IFN treatment (*P*=0.021). Fifty-one patients out of a total of 125 patients (40.8 %) with glucose intolerance had a past history of IFN treatment, which was significantly higher than the 66 patients out of 234 patients (28.2 %) with normal fasting glucose (*P*=0.021). There was no significant difference in gender and in relation to the presence of cirrhosis between the two groups (Table 1).

Dependent variable associated with glucose intolerance

Age, gender, BMI, family history of diabetes, the presence of liver cirrhosis and previous IFN treatment were identified as independent variables in a logistic regression analysis with the glucose intolerance as the dependent variable. Continuous variables were transformed into categorical variables with the cut-off determined by the Receiver Operating Characteristic curve. Stepwise multivariate logistic regression analysis revealed that age ≥57 years, the presence of family history of diabetes, obesity and previous IFN treatment were significant as independent predictive variables associated with the presence of glucose intolerance in patients with chronic hepatitis C (Table 2).

Table 2 Significant predictive variables of glucose intolerance in chronic hepatitis C patients using stepwise multivariate logistic regression analysis

	Coefficient	Odds ratio	95% CI	*P* value
Age 57 years	1.251	3.50	2.06-5.92	<0.001
Diabetic family history	1.289	3.64	2.00-6.57	<0.001
Obesity	0.576	1.78	1.05-3.03	0.034
Previous interferon treatment	0.803	2.23	1.34-3.72	0.002

Denotes: CI: confidence interval.

DISCUSSION

The close relationship between DM and chronic HCV infection had been reported in several previous studies although the exact pathogenesis remains unclear[4-11]. The age-adjusted population-based prevalence of type 2 DM and IFG in Taiwan was 5.9 % and 15.7 %, respectively[27-30]. According to our results, the prevalence of DM and IFG in patients with chronic hepatitis C was 27.6 % and 7.0 %, respectively. The prevalence of glucose intolerance (DM and IFG) was significantly higher than the age-matched normal population in Taiwan.

An altered glucose metabolism had been reported in patients with chronic liver diseases and liver cirrhosis[11]. However, patients with HCV-related chronic hepatitis and liver cirrhosis demonstrated a stronger correlation than those patients with other etiologies[5,6,11]. Patients with a viral infection alone such as cytomegalovirus, Coxackie virus and mumps were reported to develop DM, but most of the reported cases were type 1 DM[31-33]. The pathogenesis of HCV-related DM remains mysterious.

Although the close relationship between DM and chronic HCV infection has been noted, the risk factors of DM including age, sex, the presence of family history of diabetes, BMI, liver cirrhosis, and previous history of IFN treatment has not been well investigated in previous case-control studies. In the general population, male gender, older age, obesity and the presence of family history of diabetes were well recognized as significant risk factors for the development of DM. According to our results, all these risk factors except the male gender remained independent risk factors associated with the presence of DM in chronic hepatitis C patients. These findings indicated that multiple factors may contribute to the development of DM in patients with chronic hepatitis C.

Of particular interest, our results showed significantly that previous IFN treatment was an independent risk factor for the development of glucose intolerance in patients with chronic hepatitis C. IFN had been widely used in the treatment of patients with chronic hepatitis C[12-16]. Development of DM or the exacerbation of previously stable glycemic control in diabetic patients had been reported as drug side effects in chronic hepatitis C patients who were receiving IFN treatment, but the mechanism of this phenomenon remains unknown[17-19]. The presence of islet cell autoantibodies had ever been reported in a chronic hepatitis C patient during IFN treatment[34]. Fabris *et al* reported that the development of DM during IFN treatment was resulted from the amplification of previously existing autoimmunity against pancreatic β cells[35]. However, a report contradicting these findings was published later[36].

Koivisto *et al* also postulated that impaired glucose tolerance was found in healthy volunteers who received IFN treatment, and this phenomenon may have resulted from the development of insulin resistance through the complex interaction between insulin and its counter-regulatory hormones[37]. However, by using a minimal model, IFN-α injection was reported to ameliorate the glucose tolerance in diabetic and non-diabetic patients with chronic HCV infection[38]. Our results showed that previous IFN therapy can be used significantly as an independent variable to predict the development of glucose intolerance in patients with chronic hepatitis C. Patients enrolled in our study received various forms of IFN with different dosages and durations. Therefore, further evaluations are needed to clarify the enigmatic association between IFN treatment and DM development in patients with chronic hepatitis C.

In conclusion, 34.6 % of patients with chronic hepatitis C were glucose intolerant. Chronic hepatitis C patients who were older in age, were obese, and had a previous history of IFN treatment as well as a family history of diabetes were prone to develop glucose intolerance. To our best knowledge, this is the first population-based report to confirm that interferon treatment to be an independent risk factor to develop glucose intolerance.

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