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Serum retinol-binding protein 4 is inversely correlated with disease severity of chronic hepatitis C☆

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***Background/Aims*: Hepatitis C virus (HCV) infection carries a significant risk for development of insulin resistance (IR) and/or diabetes mellitus. Recently, retinol-binding protein 4 (RBP4) has been reported as a protein contributing to IR. This study aimed to assess the correlation between RBP4 and disease severity of chronic HCV infection (CHC).**

***Methods*: Serum RBP4 was measured in 105 treatment-naïve CHC patients and its correlation with the homeostasis model assessment of insulin resistance index (HOMA-IR), liver histology, virology and metabolic factors was investigated. Patients were stratified into different stages of glucose tolerance by oral glucose tolerance test.**

***Results*: There was a significant decreasing linear trend of RBP4 dependent on both histological grading (from 35.8 ± 16.5 μg/mL of minimal to 19.2 ± 12.5 μg/mL of severe, $P = 0.002$) and staging (from 34.2 ± 10.0 μg/mL of F0 to 22.2 ± 11.9 μg/mL of F3-4, $P = 0.02$) progression, whilst a significant increment of HOMA-IR was found. Multivariate regression analysis showed BMI (1.1, 95% CI 0.44 ∼ 1.77, $P = 0.001$), HDL-C (−0.40, 95% CI −0.73 ∼ −0.06, $P = 0.02$), and LDL-C (0.31, 95% CI 0.02 ∼ 0.61, $P = 0.04$) were the significant variables for prediction of RBP4.**

***Conclusions*: Disease severity may limit the role of RBP4 as a predictor of IR in CHC.**

***Keywords*: Retinol-binding protein 4; Hepatitis C virus; Insulin resistance; Liver histology**

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Abbreviations: RBP4, retinol-binding protein 4; HCV, hepatitis C virus; IR, insulin resistance; CHC, chronic HCV infection; HOMA-IR, the homeostasis model assessment of insulin resistance index; DM, diabetes mellitus; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; ALT, alanine aminotransferase; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; IFG, impaired fasting glucose; BMI, body mass index.

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1. Introduction

Hepatitis C virus (HCV) infection is one of the principle causes of cirrhosis and hepatocellular carcinoma and has a strong impact on public health worldwide. Apart from its hepatotropic characteristic, HCV infection carries a significant pathogenic effect for development of insulin resistance (IR) and/or subsequent type 2 diabetes mellitus (DM) [1–5]. Our previous studies showed that 37.8% of chronic HCV infection (CHC) patients had DM. For those patients without previously diagnosed DM, there was a 3.5-fold increase in the prevalence of glucose abnormalities in CHC patients in comparison with controls with oral glucose tolerance test (OGTT) [5,6]. In addition, IR and DM may undermine the treatment response to antiviral therapy and the disease progression of HCV infection [7]. Therefore, measurement of IR appears to be a feasible and plausible method for disease outcome assessment in patients with HCV infection.

Recently, Yang et al. identified retinol-binding protein 4 (RBP4), a circulating protein that was highly expressed in the adipose tissue of the adipocyte-specific glucose transporter 4 knockout mouse [8]. IR was induced in mice that were either overexpressing RBP4 or were injected with recombinant RBP4, whereas RBP4 knockout mice showed increased insulin sensitivity. Furthermore, an insulin-sensitizing drug (rosiglitazone) reduced the elevated levels of RBP4 in both adipose tissue and serum in their animal study. Reducing serum RBP4 levels ameliorated IR in mice fed a high-fat diet. Graham et al. extended this research to humans and showed a correlation between RBP4 levels and the magnitude of IR in subjects with obesity, impaired glucose tolerance (IGT), or DM [9]. Serum RBP4 levels were even increased in healthy adults with a strong family history of DM. All these interesting findings indicate that RBP4 may serve as a new marker for IR emergence. However, inconsistent observations have emerged simultaneously [10–13]. Although the precise mechanisms whereby HCV infection leads to IR and glucose abnormalities are not fully clear, HCV infection *per se* might provide a better viewpoint addressing the issue of the possible concealed player of RBP4 in the development of IR. However, the correlation between RBP4 and HCV infection has rarely been investigated. Meanwhile, the impact of disease progression and severity on RBP4 in HCV infection deserves to be clarified.

This study aimed to determine the correlation between serum RBP4 level and different stages of glucose tolerance and to assess the role of RBP4 in the disease severity in CHC patients. The related clinical, virological, and histological features regarding to alterations of serum RBP4 level in CHC patients were also analyzed.

2. Methods

2.1. Patient selection

2.1.1. CHC patients

From August 2006 through May 2007, 105 consecutive CHC patients (male = 47, mean age = 54.4 ± 11.0 years) were enrolled. Eligible patients were previously untreated Taiwanese patients with CHC, aged 18–65 years, who (1) were seropositive for HCV antibodies (anti-HCV) and HCV RNA; (2) had undergone a liver biopsy within 6 months before entry, the result of which was consistent with chronic hepatitis. Patients with hepatitis B surface antigen (HBsAg) seropositive, HIV infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson's disease, α1-anti-trypsin deficiency, current alcohol abuse or history of alcohol misuse (>20 g/day), were excluded from the study.

2.1.2. Community-based controls

A total of 131 healthy adults were invited for OGTT and RBP4 examinations during the multi-purpose health surveillance. The subjects were recruited either from The Clinic of Department of Preventive Medicine, Kaohsiung Medical University Hospital, or from 2 primary care stations in Kaohsiung for health survey. After excluding those anti-HCV (+) (6, 4.6%) or HBsAg (+) (12, 9.2%) subjects, those who refused examination (10, 1.3%), and those with extreme age distribution (3, 2.3%), a total of 100 sex- and age-matched adults aged 30 years or more constituted the control pool. A total of 29 subjects had history of T2DM or had previously been treated with medications for T2DM. The community-based controls consisted of 42 men (39.6%) with a mean age of 54.2 ± 9.6 years.

2.2. Study design

The ethical committee of the Kaohsiung Medical University Hospital approved the study before it began. Written informed consent for interview, anthropomorphic measurements, blood sampling, and medical record review were obtained from patients prior to enrollment. All CHC patients underwent a 12-h overnight fast before blood tests, which included HCV RNA quantitative and genotype tests, fasting plasma glucose (FPG), insulin, cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), ALT, and RBP4 levels. Control subjects were examined for FPG and RBP4 levels. Anthropometric data, including body weight, and height, were measured using standardized techniques. A questionnaire regarding the medical history, drug history, and family history was performed by research staff.

All patients and control subjects without known DM received a 75-g OGTT and then 2-h post load plasma glucose level was measured. The definition of impaired fasting glucose (IFG), IGT, and DM were made according to the American Diabetes Association criteria [14]. Briefly, patients with twice the FPG levels > 126 mg/dL of previous medical records, previously established diagnosis of T2DM, and currently taking any form of hypoglycemic drugs or insulin injections were categorized as having known DM. IFG was diagnosed if the FPG was between 100 and 126 mg/dL. Based on the OGTT results, DM and IGT were diagnosed according to a 2-h plasma glucose concentration of ⩾200 mg/dL and 140–200 mg/dL, respectively.

IR was calculated on the basis of FPG and insulin levels, according to the homeostasis model assessment (HOMA) method [15]. The formula for the HOMA model of IR is as follows: (HOMA-IR) = FPG (mg/dL) × fasting insulin level (μU/mL)/405.

Metabolic syndrome was defined based on the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian-Americans, modified by the criteria of obesity proposed for Asians by the Steering Committee of the Regional Office for the Western Pacific Region of WHO [16,17] as presenting at least three of the following components: (1) waist circumferences >90 cm in men or >80 cm in women; (2) TG > 150 mg/dL; (3) HDL-C < 40 mg/dL in men or <50 mg/dL in women; (4) blood pressure