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ARTICLE

Insulin resistance and early virological response in chronic HCV infection

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KEYWORDS

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Abstract *Background:* Studies revealed that insulin resistance is associated with fibrosis progression and has negative impact on sustained virological response after standard antiviral therapy in patients with chronic hepatitis C (CHC).

Aim: To assess the role of IR on progression of liver fibrosis and early virological response (EVR) rates in patients with chronic hepatitis C infection.

Patients and methods: The study population comprised 79 subjects who underwent combination therapy for CHC. Laboratory investigations in the form of glucose, insulin, bilirubin, alanine aminotransferase (ALT), cholesterol and triglycerides and liver biopsy were done for all patients. Insulin resistance was calculated using the homeostasis model of IR (HOMA-IR).

Results: IR was increased (>2 IU) in 31 (40.7%) of patients. Early virological response was achieved among 37 patients (48.7%). No difference in EVR, viral load or grade of liver fibrosis between patients with and without IR. A significant positive correlation was found between IR and liver steatosis.

Conclusion: Insulin resistance is a common finding in CHC, it is associated with increase liver steatosis. However it has no impact on EVR to combined interferon ribavirin therapy, viral load or necroinflammation.

1. Introduction

Insulin resistance (IR) is a condition in which higher than normal insulin concentrations are needed to achieve normal metabolic responses, or in which normal insulin concentrations fail to elicit a normal metabolic response [1].

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Insulin resistance is considered the main underlying cause of metabolic syndrome, and the main pathogenetic factor for non alcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome [2].

Recently, several studies are focused on the relationship of insulin resistance and chronic hepatitis C (CHC). Different lines of evidence have found that IR is a common feature in patients with CHC especially with genotypes 1 and 4 [3,4]. Studies in animal models using genotype 1 constructs revealed that the development of IR occurred early and in the absence of liver injury or body weight gain, providing support for a direct link between CHC infection and IR [5]. The clinical relevance of IR in HCV arises from its ability to promote hepatic inflammation and fibrosis and to impair response to antiviral therapy [4,6].

However, Contrasting data exist on the role of IR as a predictor of sustained virological response (SVR) in the setting of both HCV mono-infected and HIV/HCV coinfected subjects [7–9].

The reference method for assessment of IR is the glucose clamp technique; however this method is expensive and laborious. The homeostasis model assessment (HOMA) of insulin sensitivity was proposed as a simple and inexpensive alternative and is a good reflection of that assessed by the glucose clamp technique [10].

EVR (Early Virological Response): EVR means that hepatitis C viral load has dropped by 99% (2logs), or is undetectable after 12 weeks of HCV treatment. An EVR is a good predictor of the ultimate response to HCV treatment. If a person does not have an EVR, their chance of SVR is very low (1–4%). Usually, HCV treatment is discontinued in people who do not have an EVR [11].

The aim of the study was to assess the effect of insulin resistance, measured by HOMA test for insulin sensitivity, on the early virological response to hepatitis C virus therapy in HCV infected patients.

2. Patients and methods

2.1. Patients

We prospectively evaluated 76 patients with chronic HCV infection recruited from National Liver and Tropical Disease Institute. Patients were subjected to detailed history and clinical examination. Liver biopsy and laboratory investigations were done for all patients before starting therapy. All patients were enrolled in the study after signing the informed consent and approval of ethical committee in national research center.

Patients were initiated on treatment with subcutaneous pegylated interferon alfa-2a (180 μg/week) plus oral ribavirin (1000 or 1200 mg/day).

Exclusion criteria were: patients with hepatitis B infection or human immunodeficiency virus infection, autoimmune or metabolic liver diseases, diabetes mellitus, patients with body mass index (BMI) $\geqslant 30\ kg/m^2$, patients not eligible for interferon therapy. Also we excluded patients who were previously treated by any drug that may affect the results.

The end point was to assess early virological response and its relation to IR. Early virological response (EVR) was defined as HCV RNA undetectable at week 12.

2.2. Laboratory assessment

Blood samples were collected after a 12-h overnight fast and deposited in dry tubes with EDTA. The plasma was separated immediately using refrigerated centrifugation at 2500–3000 rpm for a period of 10 min. The samples were processed after conservation at −20 °C. Blood was collected for the determination of the serum levels of plasma glucose, insulin and alanine aminotransferase (ALT), cholesterol, triglycerides were measured after precipitation with polyanions Plasma glucose was measured immediately on fresh samples collected in oxalate tubes. Serum insulin was determined by a radioimmunoassay (Phasdaseph Insulin RIA; Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden) [12].

Insulin resistance (IR) was calculated using the homeostasis model of IR (HOMA-IR).

HOMA-IR = fasting glucose (mmol/L) × fasting insulin (μU/ml)/22.5 [12,13]. Patients with HOMA IR > 2 were considered to have IR [14].

Hepatitis CV RNA was assessed before and 12 weeks after therapy. Viral load less than 10^6 copies/ml was considered mild viremia, between 10^6 and 10^8 copies/ml moderate viremia, more than 10^8 copies/ml severe viremia.

2.3. Histopathological examination

An ultrasound guided percutaneous liver biopsy was performed for all subjects. The degree of necroinflammatory activity and of fibrosis was scored by an expert hepatopathologist based on the Ishak score [15] (F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, cirrhosis). Necroinflammation scored from 6 to 14. Hepatic steatosis was scored as the percentage of hepatocytes containing macrovesicular fat droplets. The grading was conducted as follows: grade 0, no steatosis; grade 1, < 33% of hepatocytes affected; grade 2, 33–66% of hepatocytes affected; grade 3, > 66% of hepatocytes affected [16].

2.4. Statistical analysis

Data were presented as mean and standard deviation (SD) and percentage. The data were analyzed by SPSS version 14 (SPSS Inc., Chicago, IL, USA). The following tests of significance were used: *t*-test between means to analyze differences between

Table 1 Demographic and laboratory characteristics of the patients.

	Mean ± SD	Range
Age, years	47 ± 12	18–70
BMI, kg/m^2	25.6 ± 1.5	22.5–29.7
Waist,cm	84.6 ± 6.3	68–94
ALT, IU/dl	55.8 ± 48.9	10–250
Triglycerides, mg/dl	196.2 ± 121.6	135–123
Cholesterol, mg/dl	213.8 ± 24.4	159–373
FBG, mmol/L	4.9 ± 0.6	3.8–6.7
HOMA-IR	2.6 ± 5	0.2–12.8

BMI, body mass index; ALT, alanine aminotransferase; FBG, fating blood glucose; HOMA-IR, homeostasis model assessment; IR, insulin resistance.