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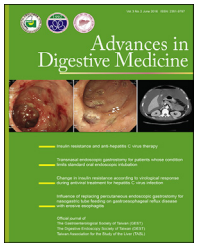

ORIGINAL ARTICLE

Change in insulin resistance according to virological response during antiviral treatment for hepatitis C virus infection

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KEYWORDS
Hepatitis C;
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Summary *Background:* Hepatitis C virus (HCV) infection can lead to increased insulin resistance, but the dynamics of insulin resistance in HCV-infected patients receiving pegylated interferon plus ribavirin remain elusive.
Methods: This prospective study enrolled HCV-infected patients who received pegylated interferon plus ribavirin. Patients were classified according to the attainment of sustained virological response (SVR). Insulin resistance was measured using homeostatic model assessment-insulin resistance (HOMA-IR). The change in HOMA-IR at baseline, the end of treatment, and 24 weeks after the end of treatment was compared in patients who achieved SVR and those who did not.
Results: A total of 65 patients participated in this study, of which 46 (71%) achieved SVR. Overall, The HOMA-IR changed significantly during antiviral therapy, with the median values [interquartile range (IQR)] of 3.7 (1.6–10.0) prior to the treatment, 1.5 (0.8–2.9) at the end, and 1.6 (0.9–3.1) at 24 weeks after completion of therapy. However, only patients who achieved SVR had significant off-therapy reduction of HOMA-IR, with median values of 1.3 (IQR, 0.7–2.6) at 24 weeks off therapy and 3.6 (IQR, 1.5–9.9) at baseline ($p < 0.0001$). In those without SVR, the HOMA-IR measured 24 weeks after treatment completion (median, 2.2; IQR, 1.9–4.7) did not differ from baseline values (median, 3.9; IQR, 2.2–10.0; $p = 0.5$).

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Conclusion: Dual therapy with pegylated interferon plus ribavirin ameliorated IR in HCV-infected patients, but the off-therapy improvement of IR was limited to those who attained SVR.

Introduction

Hepatitis C virus (HCV) infection is causally associated with impaired glucose homeostasis. Epidemiological surveys have consistently revealed a higher prevalence of insulin resistance and diabetes mellitus (DM) in HCV-infected patients than in the general population or in those with other chronic liver diseases [1—9]. HCV infection may cause insulin resistance, which is the essential component of metabolic syndrome and type 2 DM, through the direct involvement of viral proteins or as an indirect consequence of infection-related cytokine dysregulation [8,10—13].

Because chronic HCV infection is causally associated with impaired glucose homeostasis, it is plausible that viral clearance may ameliorate insulin resistance and prevent DM. Current evidence, however, remains inconclusive in confirming the efficacy of successful HCV eradication in improving glucose intolerance. Several follow-up studies observing treated patients have reported encouraging results by demonstrating a lower incidence of new-onset type 2 DM in HCV-infected patients who achieved sustained virological response (SVR), as compared with those who could not clear the virus [14—16]. Nevertheless, these studies could not ascertain whether the apparent reduction of DM incidence was the result of viral eradication or simply reflected that patients who were more likely to develop DM were more difficult to treat. Several studies showed that HCV-infected patients with insulin resistance were more difficult to treat [17,18]. In order to elucidate how antiviral treatment as well as viral clearance may impact the glucose homeostasis in patients with HCV infection, it is imperative to measure insulin resistance alongside the therapeutic course.

We conducted this study to explore the change in insulin resistance from the baseline, through the end of, and to 24 weeks after the standard regimen with pegylated interferon plus ribavirin. The association between viral clearance and amelioration of insulin resistance was assessed.

Patients and methods

Study design and patient population

This is a prospective cohort study of HCV-infected patients receiving standard antiviral therapy in a regional teaching hospital in southern Taiwan (E-Da Hospital, Kaohsiung, Taiwan). The study protocol was approved by the Institutional Review Board of E-Da Hospital (EMRP-099-112). Patients were eligible if they were older than 20 years, were seropositive for HCV antibody, had detectable HCV RNA in serum, and had elevated serum alanine aminotransferase. Those who met any of the following exclusion criteria were not enrolled: coinfection with human immunodeficiency virus or hepatitis B virus, alcohol abuse (daily consumption converted to more than 40 mL pure ethanol), presence of other concomitant liver diseases (hemochromatosis, Wilson disease, drug-related hepatitis, or alpha-1 antitrypsin deficiency), pregnant or lactating women, severe comorbidity (malignancy, major psychiatric disorder, or failure of vital organ), contraindication for interferon-based therapy, and lack of informed consent.

Antiviral therapy

All patients were treated with response-guided pegylated interferon alpha-2b (1.5 μg/kg per week; PEG-Intron; Schering-Plough Inc., Kenilworth, NJ, USA) and ribavirin (Rebetol; Schering-Plough Inc., Las Piedras, Puerto Rico) with dosage adjusted on the basis of body weight (1200 mg/d for weight $\geq$ 100 kg; 1000 mg/d for weight $<$ 75 kg). Patients who achieved rapid virological response received a 24-week therapy; those who failed to attain rapid virological response but could achieve early virological response were treated for 48 weeks. Undetectable HCV RNA 24 weeks after the completion of therapy defined the achievement of SVR. The HCV RNA test was performed at a central laboratory (Taipei Institute of Pathology, Taipei, Taiwan) for HCV RN level using second-generation real-time polymerase chain reaction assay (COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, version 2.0; Roche Molecular Diagnostics, Branchburg, NJ, USA; detection limit,15 IU/mL) and for HCV RNA genotype by LINEAR ARRAY Hepatitis C Virus Genotyping Test (Roche Molecular Diagnostics, Branchburg, NJ, USA).

Methods of measurement and definition of insulin resistance

Prior to the antiviral therapy, patients were interviewed and physically examined to obtain comprehensive personal information. Body mass index (BMI) was calculated as the patient's weight in kilograms divided by the square of height in meters. HCV genotyping was performed according to Simmonds' system.

Venous blood for laboratory examinations was collected in the morning after an overnight fast at baseline, at the end of the therapy, and 24 weeks after the cession of therapy. Insulin resistance was measured indirectly with homeostasis model assessment (HOMA-IR) method using the following formula:

fasting glucose (mg/dL) $\times$ fasting IRI (μU/mL)/405.