Metabolic syndrome is associated with poor treatment response to antiviral therapy in chronic hepatitis C genotype 3 patients

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Introduction **Hepatitis C viral (HCV) infection is caused by an RNA virus. HCV infection is considered to induce systemic disease that causes steatosis, alters lipid metabolism, and results in metabolic syndrome. This study aimed to investigate the therapeutic outcome in HCV genotype 3 patients with metabolic syndrome.**

Materials and methods **A total of 621 HCV-positive patients who visited the hospital for treatment were screened. Among these, 441 patients were enrolled for antiviral therapy. These enrolled patients were assessed for metabolic syndrome according to the International Diabetes Federation criteria. Group A included patients with metabolic syndrome and group B included patients without metabolic syndrome. All patients received peginterferon-α2a (180 μg/week) and ribavirin (10 mg/kg/day) for 6 months.**

Results **The prevalence of metabolic syndrome in chronic HCV patients was 37.9%. We observed that metabolic syndrome was more common among female compared with male participants (43.9 vs. 28.8%, $P=0.005$). It was found that sustained virologic response (SVR) rates were significantly higher in the patients in group B (without metabolic syndrome) compared with the patients in group A who had metabolic syndrome (72.2 vs. 43.7%, $P<0.05$). Older patients were at a higher risk for metabolic syndrome and a correlation of metabolic syndrome with nonresponse to antiviral therapy was observed. An interesting correlation among metabolic syndrome, age, and SVR was found: with age, SVR decreases, while metabolic syndrome increases.**

Conclusion **Metabolic syndrome has an influence on therapeutic outcomes in terms of SVR. Moreover, this information can identify patients who might have a low chance of attaining an SVR and a timely decision may protect the patients from the adverse effects of therapy.** *Eur J Gastroenterol Hepatol* **26:538–543 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Hepatitis C viral (HCV) infection is caused by an RNA virus, which is a member of the Flaviviridae and represents the major pathological agent responsible for liver disease worldwide. About 180 million individuals are estimated worldwide to have infection with HCV, which covers roughly 3% of the world's population [1]. In Asian-Pacific regions, the burden of HCV infection ranges from 0.3 to 12% [2] and in developing countries such as Pakistan, 4.8% individuals are living with HCV, with high morbidity and mortality [3]. The immune system partially controls the viral infection, but the long-lasting hepatic impact of hepatitis C infection frequently leads to hepatic steatosis to fibrosis, cirrhosis, hepatocellular cancer, and eventually liver failure [4,5]. In light of the above, the main aim is to eradicate the virus using standard of care, peginterferon (PEG-IFN) plus ribavirin. Successful treatment results in the prevention of hepatocellular carcinoma by eradication of the virus and helps in attaining a sustained virologic response (SVR), defined as an undetectable serum HCV RNA level 6 months after the end of treatment.

Although treatment response is not uniform in an HCV-infected population, primarily epidemiological, viral, and host factors have been associated with the outcome of treatment. Several studies have reported that the HCV genotype is an important predictor of treatment response; therefore, treatment duration for HCV is based on HCV genotypes, and 24 weeks are recommended for genotype 2 or 3 and 48 weeks for genotype 1 or 4 [6–8]. HCV infection has been known to induce systemic disease including insulin resistance, induced steatosis, and altered lipid metabolism, resulting in metabolic syndrome [9]. Metabolic syndrome has several manifestations including high BMI, altered glucose, fat metabolism, and hypertension (high blood pressure).

Several studies have shown that most important parameters are the HCV genotype and pretreatment HCV RNA level [10–12]; other studies have reported no significant difference between sexes in terms of antiviral

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response. However, very few studies are available worldwide in which metabolic syndrome has been analyzed [13,14]. However, this issue has not been addressed as a prognostic factor in a Pakistani HCV-infected population. This study aimed to investigate how metabolic syndrome affects the response to therapy in treatment-naive HCV patients.

Materials and methods

Study design

This study was carried out at Maroof International Hospital from May 2009 to June 2012. The study design and protocol were approved by the Digestive Disease Study Group of Maroof International Hospital and informed written consent was obtained from all the participants. A total of 621 HCV-positive patients were screened who visited the hospital for treatment and had HCV RNA for more than 6 months, had elevated serum alanine aminotransferase (ALT) at least twice the upper limit of normal on two occasions within the previous 6 months, HCV genotype 3, age above 16 years, and negative for hepatitis B. Among these, 441 patients fulfilled the study criteria and were enrolled for antiviral therapy. These enrolled patients were further assessed for metabolic syndrome according to the International Diabetes Federation (IDF) criteria [15,16]. In this study of a Pakistani population, we used the Asian cutoff for obesity, that is, at least 25 kg/m^2 [17]. In addition, they may have any of the two from the following four factors: (a) elevated triglycerides, $\geq$ 150 mg/dl (1.69 mmol/l); (b) reduced high-density lipoprotein cholesterol, <40 mg/dl (1.04 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women; (c) increased blood pressure, $\geq$ 130/85 mmHg; and (d) increased plasma fasting glucose, $\geq$ 130 mg/dl ($\geq$ 6.1 mmol/l). We divided these patients into two groups. Group A included HCV patients with metabolic syndrome [fasting plasma glucose > 130 mg, blood pressure > 130/90 mmHg or use of antihypertensive drugs, triglyceride > 150 mg/dl, central obesity with waist circumference > 104 cm (men) or >90 cm (women)]. Group B included HCV patients who did not have metabolic syndrome.

Therapeutic protocol

All patients received a combination treatment of PEG-IFN-α2a (180 μg/week) and ribavirin (10 mg/kg/day) for a duration of 6 months.

Laboratory and clinical assessment

The IDF criteria were used to diagnose the metabolic syndrome in HCV patients. The study participants were subjected to a clinical assessment after obtaining informed written consent. A detailed assessment of medical history was performed using a questionnaire and a clinical examination including assessment of BMI [BMI was calculated as weight divided by square of height (kg/m^2)], waist circumference, and blood pressure was performed according to the guidelines of the European Society of Hypertension. Fasting glucose, triglyceride, total cholesterol, high-density lipoprotein cholesterol, and HbA1c were measured on a Cobas C system (Roche Diagnostics, Mannheim, Germany). A patient was considered diabetic if fasting plasma glucose was higher than 7.0 mmol/l and/or HbA1c was 6.5% (48 mmol/mol). The HbA1c levels that we report are expressed as national glycohemoglobin standardization program levels (%). Moreover, participants who were on antihypertensive or antidiabetic drugs were considered as hypertensive and diabetics. Other baseline tests including patients' complete blood count, ALT, quantitative HCV RNA, and genotype were performed. All patients in the study were required to have hemoglobin levels above 13 g/dl in men and 12 g/dl in women. In addition, they were required to have a white blood cell count greater than 3000/mm^3 and platelet count of at least 100 000/mm^3.

The HCV RNA level was assessed in the serum using the COBAS AmpliPrep/COBAS TaqMan 48 system (with a lower limit of detection, 15 IU/ml; Roche Molecular Systems, Pleasanton, California, USA) at baseline, after 4 weeks of treatment, 12 weeks of treatment, end of the treatment, and 24 weeks after the end of the treatment. The TWT Invader assay was used for HCV genotyping, developed by Third Wave Technologies Inc. (Madison, Wisconsin, USA) [18].

Assessment of efficacy

The primary end point of this study was to assess SVR, which is defined as undetectable HCV RNA 6 months after the end of treatment, and nonresponders were those who had less than 2 log decrease in HCV RNA at week 12 of treatment. Rapid virological response (RVR) is defined as undetectable HCV RNA at 4 weeks of treatment. Patient relapse was defined as the reappearance of HCV RNA during the follow-up period in patients who achieved negative HCV RNA at the end of treatment.

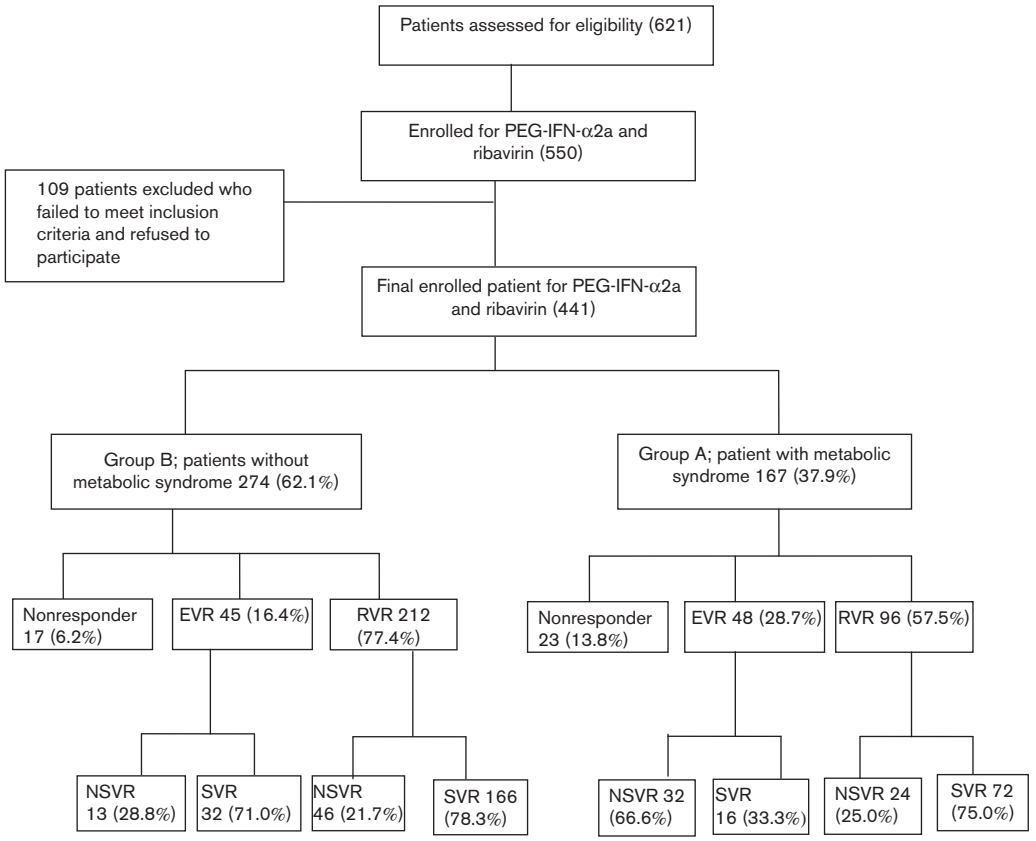
Statistical analysis

SPSS v. 15.0 (SPSS Inc., Chicago, Illinois, USA) was used for analysis. Categorical variables are expressed as the number and percentage. The Pearson χ^2 method was used for estimation of significant differences between categorical variables. A P value below 0.05 was considered significant. Univariate and multivariate logistic regression analyses were carried out to predict potential variables.

Results

In all, 620 patients were reviewed for the study. In the final analysis, 441 patients had completed 24 weeks of treatment and follow-up. A total of 167 patients were included in group A (patients with metabolic syndrome) and 274 patients were included in group B (patients without metabolic syndrome) (Fig. 1). The prevalence of metabolic syndrome in chronic HCV patients was 37.9% (167/441). Of these 167, 51 (28.8%) were men and 116

Fig. 1



The virological response rate to treatment in both groups. Group A, HCV patients with metabolic syndrome; group B, HCV patients without metabolic syndrome. SVR, undetectable HCV RNA 6 months after cession of treatment; RVR, undetectable HCV RNA at week 4; EVR, undetectable HCV RNA and >2 $\log_{10}$ viral load at week 12. EVR, early virological response; HCV, hepatitis C virus; NSVR, no sustained virological response; PEG-IFN-α2a, peginterferon-α2a; RVR, rapid virological response; SVR, sustained virologic response.

(43.9%) were women. The baseline characteristics of patients with metabolic syndrome and without metabolic syndrome are summarized in Table 1.

In patients with metabolic syndrome (group A), the rate of RVR was 57.5% (96/167) and the rate of early virological response (EVR) was 28.7% (48/167). Twenty-three (13.8%) patients remained nonresponders when assessed after 12 weeks of therapy. The rate of SVR in patients who achieved an RVR was 75% (72/96) and the rate of SVR in patients who achieved an EVR was 33.3%. In patients without metabolic syndrome, RVR was 77.4% (212/274) and EVR was 16.4% (45/274), and 17 (6.2%) remained nonresponders. SVR among patients who achieved an RVR was 166/212 (78.3%). On comparing the SVR rates between groups, it was found that the SVR rates were significantly higher in the patients in group B (patients without metabolic syndrome) as compared with the patients in group A who had metabolic syndrome (72.2 vs. 43.7%, $P < 0.05$; Fig. 3).

Metabolic syndrome was analyzed in different age groups of patients. Patients with metabolic syndrome were older compared to patients without metabolic syndrome. We found few patients (3.5%) of 40 years of age or below with metabolic syndrome. The prevalence of metabolic syndrome was 44.3% in the age group above 40–50 years. In the age group above 50–60 years, the prevalence of metabolic syndrome was six times higher than that found in the younger age group (44.3 vs. 50%). The frequency of metabolic syndrome in the age group above 60 years was 52.6%. An interesting correlation among metabolic syndrome, age, and SVR was found: with age, SVR decreases while metabolic syndrome increases (Fig. 2). Preliminary analysis showed that age ($\leq$ 40 years), viral load ($\leq 8 \times 105$ IU/ml), response at week 4 (RVR), response at week 12 (EVR), ALT (normal ALT), fasting glucose (normal), waste (normal), and triglyceride (normal) are favorable markers for SVR (Table 2).

Predictor of sustained virologic response in hepatitis C virus patients

The effects of factors (age, sex, viral load, RVR, EVR, and metabolic syndrome) on SVR were analyzed by univariable logistic regression analysis. We found RVR with an

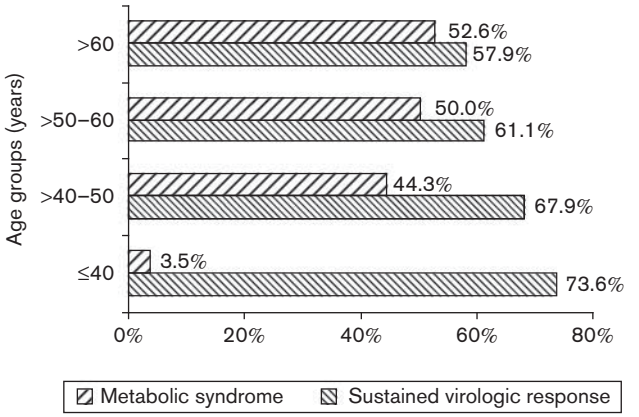
Table 1 Baseline characteristics of the patients included in the study

Patients characteristics	Total number of treated patients	Patients without metabolic syndrome [*n* (%)]	Patients with metabolic syndrome [*n* (%)]
Sex			
Male	177	126 (71.2)	51 (28.8)
Female	264	148 (56.1)	116 (43.9)
Age (years)			
≤ 40	144	139 (96.5)	5 (3.5)
>40	297	135 (45.5)	162 (54.5)
BMI (weight) (kg)			
<25	195	189 (98)	6 (3.0)
>25	246	78 (31.7)	168 (68.2)
Pretreatment ALT			
<3 × ULN	123	91 (73.9)	32 (26.4)
>3 × ULN	318	183 (57.5)	135 (42)
Pretreatment viral load (IU/ml)			
<800 000	165	82 (49.7)	83 (50.3)
>800 000	276	192 (69.6)	84 (30.41)
Fasting glucose			
Normal (≤ 130 mg/dl)	267	267 (100)	Nil
Elevated (>130 mg/dl)	174	Nil	174 (100)
Blood pressure			
Normal (≤ 130/90)	267	267 (100)	Nil
Elevated (>130/90)	174	Nil	174 (100)
Triglyceride			
Normal (≤ 150 mg/dl)	267	267 (100)	Nil
Elevated (>150 mg/dl)	174	Nil	174

ALT, alanine aminotransferase; ULN, upper limit of the normal range.

odds ratio of 4.1 (95% confidence interval, 2.68–6.37; $P = 0.001$); age of 40 years or below (odds ratio, 0.45; 95% confidence interval, 0.29–0.695; $P < 0.0001$); pretreatment viral load (odds ratio, 1.5; 95% confidence interval, 1.00–2.35; $P < 0.001$), BMI (odds ratio, 1.91; 95% confidence interval, 1.25–2.87; $P < 0.002$), pretreatment ALT (odds ratio, 0.54; 95% confidence interval, 0.35–0.83; $P < 0.006$); fasting glucose (odds ratio, 2.9; 95% confidence interval, 1.98–4.52; $P < 0.0001$); triglyceride (odds ratio, 2.9; 95% confidence interval, 1.98–4.52; $P < 0.0001$). Moreover, multivariable logistic regression analysis showed that normal fasting glucose (odds ratio, 3.0; 95% confidence interval, 3.07–1.58; $P < 0.001$); RVR (odds ratio, 3.9; 95% confidence interval, 2.47–6.14; $P < 0.0001$); low viral load (odds ratio, 2.4; 95% confidence interval, 1.45–4.04; $P < 0.001$); and metabolic syndrome (odds ratio, 3.03; 95% confidence interval, 1.56–5.87; $P < 0.001$) had a positive influence on SVR.

Fig. 2



Sustained response to peginterferon-α2a plus ribavirin treatment in different age groups of hepatitis C virus patients.

Table 2 Variables associated with sustained virologic response in hepatitis C virus patients treated with peginterferon-α2a plus ribavirin therapy

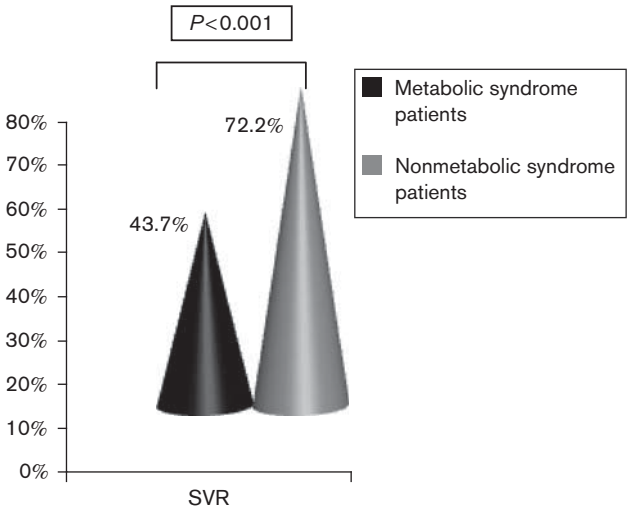
Variables	Total number of treated patients	Achieved SVR	SVR rate (%)	*P* value
Age (years)				
≤ 40	144	106	73.6	0.0001
>40	297	192	64.6	
Sex				
Male	177	116	65.5	0.45
Female	264	182	68.9	
Pretreatment viral load				
$\leq 8 \times 10^5$	165	121	73.3	0.04
$>8 \times 10^5$	276	177	64.1	
Response rate at week 4				
RVR	308	238	77.3	0.0001
NRVR	133	60	45.1	
Response rate at week 12				
EVR	405	285	70.4	0.05
Non-EVR	36	13	36.1	
Pretreatment ALT				
Elevated ALT	318	228	71.7	0.005
Normal ALT	123	70	56.9	
Fasting glucose				
Normal	275	211	76.7	0.05
Elevated	166	87	52.4	
Waste				
Normal	275	211	76.7	0.05
Elevated	166	87	52.4	
Triglyceride				
Elevated	275	211	76.7	0.05
Normal	166	87	52.4	

ALT, alanine aminotransferase; EVR, early virological response; NRVR, no rapid virological response; RVR, rapid virological response; SVR, sustained virologic response.

Discussion

The gold-standard treatment (PEG-IFN in combination with ribavirin), being expensive, causes considerable harm and many patients do not respond to treatment. In this study, all patients were evaluated for metabolic syndrome. The prevalence of metabolic syndrome in chronic HCV patients was 37.9% according to the IDF definition [19,20]. This prevalence rate is higher than that reported (24.7%) by Huang *et al.* [21] in HCV patients. The higher percentage of metabolic syndrome patients in our study may be because of the inclusion of diabetic and obese individuals as the study of Huang and colleagues did not include these. Second, some studies reported

Fig. 3



Peginterferon-α2a plus ribavirin treatment outcome in hepatitis C virus patients. SVR, sustained virologic response.

participation of the liver passively and actively in the metabolic derangements of the metabolic syndrome. HCV genotype 3 is the most common cause of hepatic steatosis because of the direct effect of its viral proteins [22].

In agreement with our study, several studies have reported the coexistence of metabolic syndrome and chronic HCV infection [23,24]. According to a few sporadic studies in the general population, the prevalence of metabolic syndrome lies between 20 and 85% [25]. In agreement with previous studies, we observed that metabolic syndrome was more common in female compared with male participants (43.9 vs. 28.8%, $P = 0.005$) [26,27]. However, this finding is in contrast to the study of Ali *et al.* [25]; they reported a higher prevalence (66%) of metabolic syndrome among men. Moreover, the prevalence of metabolic syndrome is age dependent. The same finding was also reported by Hildrum *et al.* [28].

The overall response to therapy was 67.5%, which is lower than the predicted response (75.1%) in an HCV genotype 3 Pakistani population [29] receiving gold-standard antiviral therapy. The lower response could have been because of the presence of metabolic syndrome in HCV patients. Patients with metabolic syndrome showed lower response compared with patients without metabolic syndrome (43.7 vs. 72.2%, $P = 0.0001$) (Fig. 3). This finding is in agreement with Levin [14], who showed lower response to therapy in HCV patients who had metabolic syndrome compared with HCV patients without metabolic syndrome (34.9 vs. 41.6%, $P < 0.001$). Moreover, in our study, we observed a high SVR in patients with metabolic syndrome compared with a predicted SVR of 41.6% reported by Levin and colleagues in patients with metabolic syndrome. The difference in response may be because of differences in the study population affected by different HCV genotypes [14,29]. An interesting correlation between metabolic syndrome age and SVR was found as shown in Fig. 2; with age, SVR decreases while metabolic syndrome increases [30]. Similar to other reports [31,32], we found a significantly higher percentage of SVR among patients who achieved an RVR irrespective of group A and group B. Moreover, we found lower RVR in the patients in group A than in the patients in group B (57.5 vs. 77.4%; Fig. 1).

Our finding supports the influence of metabolic syndrome on therapeutic outcomes in terms of SVR in an HCV-infected population. This will be very helpful as a high percentage of HCV-infected Pakistani individuals have metabolic syndrome. Moreover, this information can help identify patients who might have a low chance of attaining an SVR; a timely decision may protect patients from the adverse effects of therapy.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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