CLINICAL SCIENCE

Metabolic syndrome in patients with chronic hepatitis C virus genotype 1 infection who do not have obesity or type 2 diabetes

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OBJECTIVE: The individual components of metabolic syndrome may be independent predictors of mortality in patients with liver disease. We aimed to evaluate the prevalence of metabolic syndrome and its related components in hepatitis C virus–infected patients who are not obese and do not have type 2 diabetes.

METHODS: This cross-sectional study included 125 patients infected with hepatitis C virus genotype 1. Metabolic syndrome was defined according to the International Diabetes Federation. Anthropometric data were measured according to standardized procedures. Bioimpedance analysis was performed on all patients.

RESULTS: Metabolic syndrome was diagnosed in 21.6% of patients. Of the subjects with metabolic syndrome, 59.3% had hypertension, 77.8% had insulin resistance, 85.2% were overweight, 48.1% had a high waist circumference, 85.2% had an increased body fat percentage, and 92.3% had an elevated waist:hip ratio. In the bivariate analysis, female sex (OR 2.58; 95% CI: 1.09–6.25), elevated gamma-glutamyl transferase (γGT) (OR 2.63; 95% CI: 1.04–7.29), elevated fasting glucose (OR 8.05; 95% CI: 3.17-21.32), low HDL cholesterol (OR 2.80; 95% CI: 1.07–7.16), hypertriglyceridemia (OR 7.91; 95% CI: 2.88–22.71), elevated waist circumference (OR 10.33; 95% CI: 3.72–30.67), overweight (OR 11.33; 95% CI: 3.97–41.07), and increased body fat percentage (OR 8.34; 95% CI: 2.94–30.08) were independent determinants of metabolic syndrome. Using the final multivariate regression model, similar results were observed for abdominal fat (OR 9.98; 95% CI: 2.63–44.41) and total body fat percentage (OR 8.73; 95% CI: 2.33–42.34). However, metabolic syndrome risk was also high for those with blood glucose $\geq$5.55 mmol/L or HDL cholesterol $<$0.9 mmol/L (OR 16.69; 95% CI: 4.64–76.35; OR 7.23; 95% CI: 1.86–32.63, respectively).

CONCLUSION: Metabolic syndrome is highly prevalent among hepatitis C virus–infected patients without type 2 diabetes or obesity. Metabolic syndrome was significantly associated with hypertension, insulin resistance, increased abdominal fat, and overweight.

KEYWORDS: Metabolic Syndrome; Chronic Hepatitis C; Genotype 1; Overweight; Insulin Resistance.

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INTRODUCTION

Over 170 million people worldwide, constituting 3% of the global population, are infected with the hepatitis C virus (HCV) (1). In Brazil, it is estimated that 1–2% of the national population is infected with HCV (2,3).

HCV infection increases oxidative stress, tissue damage, and pro-inflammatory cytokine secretion, all of which contribute to progressive fibrosis, cirrhosis, cancer, and liver failure (4,5). Chronic hepatitis C is associated with significant morbidity and mortality and is the main reason for liver transplants in the developed world (6).

Recent data suggest a close relationship between HCV infection and metabolic syndrome (7). It is possible that HCV infection causes fatty liver disease, a precursor of hepatic steatosis, which is a recognized component of metabolic syndrome (8). Individual components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease, including those infected with HCV (9).

Metabolic syndrome is more prevalent among patients with type 2 diabetes and obesity. However, there are no data regarding metabolic syndrome in non-obese, non-diabetic

No potential conflict of interest was reported.

patients with chronic hepatitis C. In this study, we evaluated the prevalence of metabolic syndrome and its risk predictors in HCV genotype 1–infected patients who do not have obesity or type 2 diabetes.

METHODS

This cross-sectional study included 125 HCV genotype 1–infected patients who attended the Nutrition and Hepatology Clinic at the Hospital of the Federal University of Bahia. We recruited treatment-naive patients, as well as nonresponders and relapsers to antiviral therapy. All patients were over 18 years of age, consumed less than 20 g/day of alcohol and were not taking antiviral therapy or had discontinued antiviral therapy for at least three months. HCV infection was diagnosed by the presence of serum antibodies to HCV (anti-HCV), which was confirmed by qualitative determination of HCV RNA. Reverse transcription–polymerase chain reaction (RT-PCR) was performed on all samples to quantify the HCV RNA.

Patients with diabetes mellitus or obesity (BMI>30 kg/m^2) were excluded. Additionally, pregnant women and patients with HIV, HBV, renal failure, heart disease, decompensated cirrhosis, or malignancy were also excluded from the study.

All subjects signed a written informed consent. The study was approved by the ethics commitee of Federal University of Bahia according to the Declaration of Helsinki.

Complete demographic and social history data were obtained from all patients. Clinical data, such as diagnosis, viral genotype, necroinflammatory index, and presence of fibrosis, were collected from the patients' medical records. Anthropometric data, including body weight, height, and waist circumference, were measured according to standardized procedures. Waist circumference (WC) was measured according to World Health Organization (WHO) recommendations (10).

Waist circumference was measured at the midpoint between the superior aspect of the iliac crests and the lower lateral margins of the ribs using an inelastic tape (TBW Import Ltd) that was 0.5 cm in width and 200 cm in length. Additionally, multicompartmental bioimpedance analysis (model Inbody 520®) was performed according to the manufacturer's instructions. For men and women, body fat percentages ≥25% and ≥32%, respectively, were considered to increase the risk for obesity-related comorbidities (11).

After a 12-hour fast, blood samples were collected to determine serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (γGT), alkaline phosphatase (ALP), plasma glucose, insulin, triglyceride, total cholesterol, and lipoprotein fraction levels. Analyses were performed using Beckman Coulter LX20 PRO equipment and a CX-9 Chemistry Analyzer with Labtest kits. Serum insulin was measured by the electrochemiluminescence method using Elecsys 2010 equipment (Roche Kit).

The insulin resistance index was calculated according to the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR): HOMA-IR = fasting insulinemia (microU/mL) x fasting glycemia (mmol/L)/22.5) (12).

Patients underwent abdominal ultrasonography with one of three radiologists using a single machine. Hepatic steatosis was graded as mild, moderate or severe according to the classification of Saverumuttu et al. (13).

Metabolic syndrome was defined based on the International Diabetes Federation (IDF) criteria, including the presence of a waist circumference ≥90 cm for men and ≥80 cm for women plus at least two of the following: arterial blood pressure ≥130/85 mmHg or taking medications for blood pressure, triglycerides ≥150 mg/dl or taking fibrates, HDL cholesterol <40 mg/dl for men and <50 mg/dl for women or taking pharmacological therapy, and fasting glucose ≥100 mg/dl or a diagnosis of diabetes (14).

The cut-off points adopted for classifying central obesity as a predictor of increased risk for metabolic syndrome were a waist circumference >88 cm for women and >102 cm for men; these cut-offs are associated with a substantially increased risk of metabolic complications according to the WHO (10). Abdominal obesity was further defined as a waist:hip ratio (WHR) >0.90 for men and >0.85 for women. An increased WHR is associated with greater cardiovascular risk (10,15).

We used the medical record to determine whether patients had arterial hypertension. This determination included subjects who had been previously diagnosed with hypertension by their clinicians and all patients who were under pharmacological treatment.

All data were analyzed using statistical package R version 2.12 (16). Statistical analysis was performed using the Mann–Whitney test for comparisons of continuous variables between groups and the corrected Fisher's exact test for comparisons of frequencies. Logistic regression analysis was used to evaluate risk predictors for metabolic syndrome. A two-tailed p-value <0.05 was considered to be statistically significant.

RESULTS

Patient Characteristics and Prevalence of Metabolic Syndrome

Metabolic syndrome was diagnosed in 21.6% of the patients with HCV. The mean age was 53.3 years (±10.5 years), and 78 (62.4%) of the patients were male. Additionally, 74 patients (59.2%) had previously undergone antiviral treatment, and 51 (40.8%) were treatment-naive. Table 1 shows the prevalence of metabolic syndrome (MS) and the demographic, clinical, and anthropometric characteristics of the patients. Women had a higher prevalence of MS (55.6%). Among patients with metabolic syndrome, hypertension was present in 59.3%, HOMA-IR ≥3 was present in 77.8%, 85.2% were overweight, 48.1% had an increased waist circumference, 85.2% had an increased body fat percentage, and 92.3% had an elevated waist:hip ratio. There was no significant association between metabolic syndrome and hepatic steatosis, degree of liver fibrosis, age or previous treatment (nonresponders/relapsers vs. treatment-naive; $p = 0.508$). The distribution of treatment-naive patients vs. nonresponders/relapsers was similar for those with and without MS (Table 1). Of note, after logistic regression analysis, previous antiviral treatment did not appear to be a risk factor for metabolic syndrome.

Individuals with metabolic syndrome had significantly higher fasting glucose ($p = 0.0005$), fasting insulin ($p<0.0001$), HOMA-IR ($p<0.0001$), and triglycerides ($p = 0.0003$) and lower HDL ($p = 0.006$) (Table 2).

Predictors of Metabolic Syndrome

Bivariate analyses of risk factors for metabolic syndrome in this population are shown in Table 3. Women were 2.5 times more likely to have MS (OR 2.58; 95% CI: 1.09–6.25),

Table 1 - Demographic, anthropometric, clinical, and histological data in patients with chronic HCV infection.

	Metabolic syndrome		Total	*p*-value*
	Yes (n = 27)	No (n = 98)		
	n (%)	n (%)	n	
Sex				
Male	12 (44.4)	66 (67.3)	78	0.043
Female	15 (55.6)	32 (32.7)	47	
Age				
<60	19 (70.4)	69 (70.4)	88	1.000
≥60	8 (29.6)	29 (29.6)	37	
Antiviral treatment status				
Naive	9 (33.3)	42 (42.9)	51	0.507
Nonresponders/relapsers	18 (66.7)	56 (57.1)	74	
Stage of fibrosis on liver biopsy				
F0-F2	13 (56.5)	47 (61.0)	60	0.809
F3-F4	10 (43.5)	30 (39.0)	40	
Hepatic steatosis detected by abdominal ultrasound				
No	10 (52.6)	53 (67.9)	63	0.283
Yes	9 (47.4)	25 (32.1)	34	
Systemic arterial hypertension				
No	11 (40.7)	76 (77.6)	87	<0.001
Yes	16 (59.3)	22 (22.4)	38	
HOMA-IR				
<3.0	6 (22.2)	73 (74.5)	79	<0.001
≥3.0	21 (77.8)	25 (25.5)	46	
Body mass index				
<25 kg/m^2	4 (14.8)	65 (66.3)	69	<0.001
25–30.0 kg/m^2	23 (85.2)	33 (33.7)	56	
Waist circumference[a]				
Adequate	14 (51.9)	89 (90.8)	103	<0.001
Elevated	13 (48.1)	9 (9.2)	22	
Waist:hip ratio[b]				
Adequate	1 (3.7)	39 (39.8)	40	<0.001
Elevated	26 (92.3)	59 (60.2)	85	
Body fat percentage[c]				
Adequate	4 (14.8)	58 (59.2)	62	<0.001
Elevated	23 (85.2)	40 (40.8)	63	

*Fisher's exact test.
[a]Adequate WC: ≤88 cm for women and ≤102 cm for men.
[b]Adequate WHR: ≤85 cm for women and ≤90 cm for men.
[c]Adequate BF%: <32 cm for women and <25 cm for men.

and patients with γGT≥85 U/L were 2.6 times more likely to have MS (OR 2.63; 95% CI: 1.04–7.29). Fasting hyperglycemia (OR 8.05; 95% CI: 3.17–21.32), hypertriglyceridemia (OR 7.91; 95% CI: 2.88–22.71), and abnormal waist circumference (OR 10.33; 95% CI: 3.72–30.67) were major contributors to MS. Overweight (OR 11.33; 95% CI: 3.97–41.07) and increased body fat percentage (OR 8.34; 95% CI: 2.94–30.08) also contributed to metabolic syndrome. Using the final multivariate regression model, similar results were observed for abdominal fat (OR 9.98; 95% CI: 2.63–44.41) and total body-fat percentage (OR 8.73; 95% CI: 2.33–42.34). However, MS risk was higher for those with blood glucose ≥5.55 mmol/L and those with HDL cholesterol <0.9 mmol/L (OR 16.69; 95% CI: 4.64–76.35; OR 7.23; 95% CI: 1.86–32.63, respectively) (Table 4).

DISCUSSION

The prevalence of metabolic syndrome in our study was 21.6%, which is similar to the prevalence of 24.7% found by Huang et al. using the same IDF criteria. Indeed their study did not exclude diabetic and obese patients (17).

When the NCEP/ATPIII criteria were used, only 12.1% of the patients were diagnosed with metabolic syndrome (data not shown). Sersté et al. (2010) found similar results (12.4%) in a large cohort of patients with chronic hepatitis C (18). The NCEP/ATPIII criteria would not have diagnosed almost 9.5% of the individuals with MS who were diagnosed using the IDF definition (12.1% vs. 21.6%; $p<0.006$). Therefore, we chose to use the IDF definition of metabolic syndrome, which adopts lower waist circumference and fasting glucose cut-offs to define obesity and hyperglycemia.

It should be noted that even after excluding patients with diabetes and obesity, there was a high prevalence of metabolic syndrome among patients with chronic hepatitis C. These patients also presented a significantly higher percentage of total body fat, waist circumference, waist:hip ratio and BMI compared to those without MS. In the present study, MS patients had significantly higher BMI than others. These results are in agreement with a study conducted in Taiwan that demonstrated that patients with hepatitis B and C and MS, as defined by NCEP/ATP III criteria, had higher BMI compared to those without MS (19).

Table 2 - Median values for biochemical tests and HOMA-IR in patients with chronic HCV infection.

	Metabolic syndrome				*p*-value*
	Yes (n = 27)		No (n = 98)		
	md	i iq	md	i iq	
Total cholesterol (mmol/L) [1]	3.47	1.27	4.07	1.18	0.4009
LDL-c (mmol/L) [1]	1.99	1.13	2.45	1.09	0.2493
HDL-c (mmol/L) [1]	1.04	0.37	1.17	0.40	0.0063
Triglycerides (mmol/L) [2]	1.56	0.75	0.99	0.56	0.0003
Aspartate Aminotransferase (U/L)	71.0	47.7	53.5	43.7	0.1778
Alanine Aminotransferase (U/L)	81.0	41.5	68.0	47.0	0.2282
Gamma Glutamyl Transferase (U/L)	138.0	96.0	83.0	110.0	0.0974
Alkaline Phosphatase (U/L)	91.0	32.0	80.0	55.5	0.7982
HOMA-IR	4.3	2.2	2.03	1.7	<0.0001
Fasting Insulin (pmol/L) [3]	108.3	57.6	61.7	49.3	<0.0001
Fasting Glucose (mmol/L) [4]	5.72	1.22	4.99	0.65	0.0005
Body Mass Index (kg/m^2)	27.8	3.1	23.7	4.0	<0.0001

*Mann-Whitney test.
[1]mg/dL (÷0.0259), [2] mg/dL (÷0.0113), [3] μIU/mL(÷6.945), [4] mg/dL (÷0.0555).

Antiviral treatment in patients with chronic HCV infection may induce changes in body weight, insulin resistance and serum lipid levels. However, all previously treated patients in our study had stopped receiving treatment for at least 3 months and therefore were not under the effects of interferon.

In the absence of MS, patients usually had an appropriate BMI and body-fat percentage and normal insulin sensitivity. We found a mean HOMA-IR >3.0 in patients with MS. This finding is in agreement with a study by Grigoresceu et al. (20) of treatment-naive patients with HCV, which found significantly higher HOMA-IR values in patients with MS (7.88 vs. 4.29). However, those authors observed a metabolic syndrome prevalence of 61.48% using the IDF criteria. We speculate that this higher MS prevalence may be explained by the inclusion of obese patients and a greater proportion of women (65.4%); our study excluded obese subjects, and only 37.4% of our patients were women. Furthermore, those authors used a HOMA-IR value ≥2.0 to define insulin resistance and a value of ≥4 to diagnose a pre-diabetic state. If we had used those cut-off values, we would have found that most patients with hepatitis C and HOMA-IR values between 2 and 3 had insulin resistance, rather than metabolic syndrome. In addition, half of our patients with MS had a HOMA-IR value ≥4 and would have been considered pre-diabetic.

Table 3 - Independent predictors of metabolic syndrome in patients with chronic HCV infection.

	Crude OR (95% CI)	*p*-value
Sex		
Female	2.58 (1.09-6.25)	0.0326
γGT		
≥85 U/L	2.63 (1.04-7.29)	0.048
Fasting glucose		
≥5.55 mmol/L	8.05 (3.17-21.32)	<0.001
HOMA-IR		
≥3.0	10.22 (3.90-30.54)	<0.001
HDL-c		
<0.9 mmol/L	2.80 (1.07-7.16)	0.0316
Triglycerides		
≥1.7 mmol/L	7.91 (2.88-22.71)	<0.001
Body mass index		
25 - 30 kg/m^2	11.33 (3.97-41.07)	<0.001
Waist circumference[a]		
Elevated	10.33 (3.72-30.67)	<0.001
Body fat percentage[b]		
Elevated	8.34 (2.94-30.08)	0.01

[a]Elevated WC: > 88 cm for women and > 102 cm for men.
[b]Elevated BF%: ≥ 32 cm for women and ≥ 25 cm for men.

Table 4 - Multivariate analysis for predictors of metabolic syndrome in patients with chronic HCV infection.

	Adjusted OR* (95% CI)	*p*-value
Waist circumference[a]		
Elevated	9.98 (2.63-44.41)	0.0012
Body fat percentage[b]		
Elevated	8.73 (2.33-42.34)	0.0029
Fasting glucose		
≥5.55 mmol/L	16.69 (4.64-76.35)	<0.0001
HDL-c		
<0.9 mmol/L	7.23 (1.86-32.63)	0.0059

*OR adjusted for other variables shown.
[a]Elevated WC: >88 cm for women and > cm for men.
[b]Elevated BF%: ≥32% for women and ≥25 % for men.

HCV proteins can activate TNF-α expression and inhibit the function of insulin receptor substrate (IRS) proteins, which contribute to insulin resistance by decreasing glucose transporter (GLUT-4) expression and lipoprotein lipase in peripheral tissues (21). Insulin resistance has frequently been associated with steatosis, fibrosis progression and lower response to HCV antiviral therapy with PEGylated interferon and ribavirin (22-25). The data from this study suggest that the evaluation of HOMA-IR in certain patients with HCV, especially those who are overweight, might be beneficial in the early detection of abnormal glucose metabolism in this population.

In our evaluation of independent risk factors for metabolic syndrome, overweight individuals were 11 times more likely to develop MS than were non-overweight patients. When the body fat percentage criteria were considered, the risk for developing metabolic syndrome was 8.3 times higher. These data highlight the importance of body composition analysis in screening for metabolic syndrome and the importance of using a sensitive cut-off for diagnosing abdominal obesity, such as the one suggested by the IDF.

Our study also found that γGT ≥85 U/L was an independent predictor of MS; these data are consistent with the results observed by Lee et al. in the participants of the Framingham study. The authors found that an increase in serum γGT predicts the onset of metabolic syndrome, cardiovascular disease, and death, suggesting that γGT is a marker of metabolic and cardiovascular risk (26).

Although γGT is commonly used in clinical practice as an indicator of hepatobiliary disease and active ethanol consumption, this enzyme might also be used as a biomarker for metabolic syndrome and cardiovascular risk and is strongly associated with insulin resistance (27). Insulin resistance, type 2 diabetes, hypertension, obesity, and metabolic syndrome are independent predictors of mortality in individuals with hepatitis C (9,28). Our study was a cross-sectional study of adults with chronic HCV infection who were divided into two groups based on whether they had metabolic syndrome. Therefore, this study did not have a sex- and age-matched control group.

In conclusion, our study showed that 21.6% of patients infected with HCV genotype 1 had MS. MS was significantly associated with hypertension, insulin resistance, increased

abdominal fat, and overweight. Therefore, frequent monitoring for insulin resistance and weight gain among patients with HCV is beneficial because these clinical conditions can negatively affect disease prognosis. Maintaining a healthy body weight is important because it reduces the incidence of comorbidities and possibly delays the progression of chronic liver disease. Further studies are needed to evaluate whether an intervention involving lifestyle modifications and/or drug treatments for MS components can improve the response to antiviral treatments in these patients.

AUTHOR CONTRIBUTIONS

Oliveira LM designed the study, evaluated and assisted the patients, conducted the research, analyzed the data and performed the statiscal analysis and was also responsible for the manuscript writing. Jesus RP designed the study, evaluated and assisted the patients, conducted the research and was also responsible for the manuscript writing. Lyra AC designed the study, evaluated and assisted the patients and was also responsible for the manuscript writing. Lyra LG designed the study and was also responsible for the manuscript writing. Boulhosa RB evaluated and assisted the patients, conducted the research and was also responsible for the manuscript writing. Mendes CM analyzed the data and performed the statistical analysis.

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