

# Insulin resistance in non-diabetic patients with chronic hepatitis C: what does it mean?

*Resistência insulínica em portadores de hepatite crônica C não diabéticos: qual o significado?*

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## ABSTRACT

**Objectives:** To determine the prevalence of insulin resistance (IR) in non-diabetic patients with chronic hepatitis C, and to assess the association between IR, laboratory parameters and histological findings. **Subjects and methods:** Eighty-two patients had their serum analyzed for glucose, lipid profile, C-reactive protein (CRP), ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), HOMA-IR, viral load and HCV genotype. Patients with HOMA-IR levels > 2.5 were considered as carriers of insulin resistance. **Results:** IR was observed in 27% of patients and was associated with age, waist circumference and body mass index. IR patients were more likely to have more advanced hepatic fibrosis and necroinflammatory activity, higher levels of aminotransferases and liver steatosis than patients without IR. **Conclusions:** Insulin resistance is often present in patients with chronic hepatitis C, and this parameter is associated with more advanced HCV-related hepatic fibrosis. Arq Bras Endocrinol Metab. 2011;55(6):412-8

## Keywords

Chronic hepatitis C; liver fibrosis; insulin resistance; HOMA-IR

## RESUMO

**Objetivos:** Em portadores de hepatite crônica C não diabéticos, verificar a prevalência de resistência insulínica (RI) e analisar a associação desta com os parâmetros laboratoriais e histológicos. **Sujeitos e métodos:** Foram incluídos no estudo 82 pacientes, e amostras de sangue foram coletadas para determinação de glicose, perfil lipídico, alanina aminotransferase (ALT), aspartato aminotransferase (AST), ferritina, HOMA-IR, carga viral e genótipo do VHC. HOMA-IR superior a 2,5 foi considerado resistência insulínica. **Resultados:** RI foi observada em 27% dos pacientes e foi associada a idade, circunferência abdominal e índice de massa corpórea. Quando comparado a pacientes sem RI, aqueles com HOMA-IR superior a 2,5 apresentaram graus mais acentuados de fibrose hepática e atividade necroinflamatória, maiores níveis de aminotransferases e esteatose hepática mais frequente. **Conclusões:** É comum a presença de RI em portadores de hepatite crônica C e esta se associa com graus mais avançados de fibrose hepática induzida pelo vírus da hepatite C. Arq Bras Endocrinol Metab. 2011;55(6):412-8

## Descritores

Hepatite crônica C; fibrose hepática; resistência insulínica; HOMA-IR

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## INTRODUCTION

Chronic hepatitis C virus (HCV) infection is the main cause of death due to liver disease worldwide, and is one of the main reasons for liver transplantation. Recent estimates indicate that 2.2% of the world population

(130 million people) are infected with HCV (1). Data from the Brazilian Society of Hepatology obtained from Brazilian blood donors have shown a prevalence rate of HCV infection equal to 1.1%, with higher rates in the North and lower rates in the South of the country (2).

Acute HCV infection is most often asymptomatic; 50-85% of these patients ultimately develop chronic hepatitis (3), and 20%-30% of HCV patients develop cirrhosis after 20-30 years of disease (4). In a recent study, John-Baptiste and cols., reported that 14.8% of the individuals who acquired HCV infection by intravenous drug use developed cirrhosis 20 years after being infected (5). The rate of progression to cirrhosis is the most important factor in the natural history of HCV infection. Once cirrhosis develops, complications due to portal hypertension account for HCV-related morbidity and mortality. Since most patients with HCV-related chronic hepatitis do not develop cirrhosis, it is logical to infer that host-related and virus-related factors must play a role in the progression to cirrhosis. In a pivotal 2001 study by Poynard and cols., host-related variables, such as male sex, age at the time of infection and excessive alcohol intake were independently associated with progression of HCV-induced liver fibrosis (6). In recent years, other factors, such as coinfection with human immunodeficiency virus (HIV), insulin resistance (IR) and hepatic steatosis, have also been linked to progression of hepatic fibrosis (7-10). In 2003, Hui and cols. studied 260 patients with HCV-related chronic hepatitis and found that the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), a marker of insulin resistance (IR), was independently associated with advanced fibrosis (8).

The importance of IR has been increasingly recognized, and its association with the metabolic syndrome (MS) – characterized by central obesity, dyslipidemia, abnormalities in glycemic control and arterial hypertension (11) – are well established, probably representing its main pathogenic mechanism. The importance of MS has been increasingly recognized in hepatology literature. Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver diseases in the western world. It is considered the hepatic manifestation of MS, and is linked to the development of liver cirrhosis and hepatocellular carcinoma (12). Because insulin primarily facilitates glucose uptake by muscles, liver, and adipose tissue, IR seems to be caused by decreased responsiveness of these tissues to physiological amounts of circulating plasma insulin (13), which may be due to genetic predisposition or acquired metabolic disorders, chiefly visceral obesity (14).

Patients with chronic liver disease, and cirrhosis in particular, are known to be prone to IR. However, chronic HCV infection may induce IR, regardless of

the presence of liver cirrhosis. Hui and cols. demonstrated that patients with chronic HCV hepatitis without liver fibrosis had increased levels of insulin, HOMA-IR and peptide C compared with metabolically-matched healthy individuals (8). Two other studies have indirectly demonstrated the cause-effect relationship between chronic HCV infection and IR. Patients with HCV-related hepatitis who had sustained virological responses after antiviral therapy were less likely to develop type 2 *diabetes mellitus* (DM2) and glycemic alterations, compared with non-responders (15,16). Although the mechanisms underlying the development of IR in patients with HCV chronic infection have not been fully elucidated, the following factors have been recently considered: changes in insulin signaling pathways due to viral proteins; chronic inflammation with overproduction of tumor necrosis factor (TNF) and consequent phosphorylation of IRS-1 serine residues, lower expression of genes related to glucose metabolism, and degradation of insulin receptor substrates (17).

Besides having higher rates of progression to liver fibrosis, patients with chronic HCV hepatitis and IR are less likely to respond to antiviral therapy (9,18-20). In Brazil, no studies have determined the rate of IR occurrence in chronically HCV-infected populations, or the consequence of such association. Thus, we aimed at assessing the prevalence rate of IR in an HCV-infected population, and the effects of this association on laboratory and histological parameters of chronic HCV-related hepatitis. Greater knowledge about this intriguing relationship and its impact may provide investigators with strategies to alter the natural history of chronic HCV hepatitis and improve the results of antiviral therapy.

## SUBJECTS AND METHODS

This was an observational and cross-sectional study, with prospective inclusion of data. After approval by the Committee of Research Ethics at the University Hospital of the Universidade Federal de Juiz de Fora (HU-UFJF), informed consent was obtained and patients were included in the study. Patients with chronic HCV hepatitis seen at the HU-UFJF Hepatology Reference Center were consecutively enrolled, from January 2010 to June 2011. The eligibility criterion was chronic HCV infection documented by positive results in qualitative HCV-RNA test. Exclusion criteria included: previous antiviral treatment, coinfection with hepati-

tis B virus (HBV) or human immunodeficiency virus (HIV I and II), chronic renal disease, type 2 DM, decompensated liver cirrhosis, hepatocellular carcinoma, and average alcohol intake greater than 20 g ethanol/day (women) and 40 g ethanol/day (men) during the preceding year.

Enrolled patients underwent clinical assessment (history and physical examination) and had blood samples drawn. The following demographic, epidemiological and clinical data were recorded on enrollment: gender, age at the time of liver biopsy, cause of HCV (blood transfusion; intravenous drug use; sexual intercourse; indeterminate causes; and other causes, such as inhaled drugs, acupuncture or surgery), blood pressure, weight, height, body mass index (BMI) and abdominal circumference.

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), albumin and fasting glucose (kinetic method), cholesterol and triglycerides (colorimetric method) were carried out with Abbott reagents. DiaSys and precipitation were employed for HDL cholesterol (HDL-c), and the Friedwald formula was employed for LDL cholesterol (LDL-c). The international normalized ratio of prothrombin time (INR) was determined with ISI and PT-Fib recombinant reagent and processed in an ACL 3000 device, with ISI determined by the manufacturer. Ferritin was measured using DiaSys reagent and chemiluminescent microparticle immunoassay methodology (CMIA). Ultra-sensitive C-reactive protein (CRP) was determined with immunoturbidimetry. Hepatitis C viral load was determined using real-time polymerase chain reaction (Abbott HCV Real Time) and HCV genotyping (Reverse transcription – polymerase chain reaction / nucleic acid sequencing). Serum insulin levels were determined using the microparticle enzyme immunoassay (MEIA), Abbott AxSYM system. The level of IR was assessed using HOMA-IR (Homeostasis model assessment of insulin resistance), calculated as fasting blood glucose [mmol/L] X fasting blood insulin [mil/L] / 22.5). IR was defined as HOMA-IR > 2.5. Biochemical analyses were performed at the HU-UFJF Central Laboratory; fasting insulin, HOMA-IR and ultra-sensitive CRP were performed at the Cortes Villela Laboratory – Juiz de Fora – MG; molecular biology assays (qualitative HCV-RNA, quantitative HCV-RNA, HCV genotyping) were performed at the Universidade Federal de Minas Gerais NUPAD Laboratory.

Histopathological assessment included: stage of fibrosis and periportal necroinflammatory activity according to the *Metavir* histological score (21), and presence of steatosis, quantified as follows: up to 5%; 5% to 33%; 33% to 66%; and over 66%, according to Brunt (22). Patients with any contraindication to liver biopsy, but with clinical, laboratory and imaging evidence of liver cirrhosis (stage 4 fibrosis) were included. All liver biopsies were analyzed by a single pathologist, experienced in liver pathology and blind to patients' clinical data.

MS was diagnosed according to the criteria of the International Federation of Diabetes (IDF), American Heart Association (AHA) and National Heart, Lung and Blood Institute (23). According to the latter, MS was diagnosed by the presence of at least three of the following symptoms: systemic arterial blood pressure (BP) > 130 x 85 mmHg; high-density lipoprotein (HDL) cholesterol < 40 mg/dL (men) and < 50 mg/dL (women); triglycerides > 150 mg/dL; fasting blood glucose > 100 mg/dL; abdominal circumference > 90 cm (men) and > 80 cm (women) (levels recommended by South and Central America populations by the International Diabetes Federation). For the analysis of the results, patients were allocated to two groups: Group I – patients with chronic HCV hepatitis without IR, and Group II – patients with chronic HCV hepatitis and IR.

### Statistical analysis

The SPSS program (15.0 for Windows) was used. Numerical variables were expressed as means ± standard deviation, and medians, when appropriate. Categorical variables were expressed as absolute (n) and relative (%) frequencies. For statistical analysis of the categorical variables, chi-square and Fisher's exact tests were used. For comparison of numerical variables between the two groups, Student "t" and Mann-Whitney tests were used. Significance level adopted was P less than 0.05 ( $\alpha = 5\%$ ).

## RESULTS

Eighty two patients (mean age of 51 years), 42 (51%) men and 40 (49%) women, were included in the study. IR and obesity were observed in 22 (27%) and 15 (18%) of them, respectively (Table 1). Patients with chronic HCV hepatitis and IR had greater mean age ( $56.9 \pm 10.1$  vs.  $49.7 \pm 12.3$ ;  $p = 0.03$ ), larger abdominal circumference ( $97.8 \pm 11.9$  vs.  $87.1 \pm 11.1$ ;

$p = 0.04$ ) and higher BMI ( $28.1 \pm 4.4$  vs.  $25.4 \pm 4.1$ ;  $p = 0.01$ ), compared with individuals without IR (Tables 1 and 2). Gender, obesity, and systemic arterial hypertension were similar between patients with and without IR. MS was present in 24 (29%) patients; 41% in the IR group vs. 25% in the group without IR, although the difference was not statistically significant (Table 1).

Patients with chronic HCV hepatitis and IR had higher levels of blood glucose ( $p = 0.004$ ), fasting insulin

( $p < 0.0001$ ) and HOMA-IR ( $p < 0.0001$ ), compared with patients without IR (Table 2). Levels of ALT ( $p = 0.03$ ), AST ( $p < 0.0001$ ), GGT ( $p = 0.03$ ) and INR ( $p = 0.02$ ) were significantly higher, and albumin levels were significantly lower ( $p = 0.003$ ) in patients with chronic HCV hepatitis and IR. There was no association between IR, viral load and HCV genotype. Of the 82 patients included in the study, only two did not undergo liver biopsy because of coagulopathy. They were considered F4 (grade 4 fibrosis), as mentioned in the inclusion criteria. Thus, 29 (36%) patients had liver fibrosis  $\geq 2$ , and nine had liver cirrhosis (F4). Patients with IR were more likely to have steatosis ( $p = 0.001$ ), higher grades of fibrosis ( $p = 0.005$ ) and periportal necroinflammatory activity ( $p = 0.04$ ). Furthermore, patients with IR had higher rates of advanced liver fibrosis (fibrosis  $\geq 2$ ;  $p = 0.007$ ), and a tendency towards higher rates of periportal necroinflammatory activity  $\geq 2$  ( $p = 0.08$ ).

**Table 1.** Demographic and anthropometric characteristics of the 82 patients according to the presence or absence of insulin resistance (IR)

Variables	N (%)	IR absent (n = 60)	IR present (n = 22)	P
Male	42 (51%)	32 (53%)	10 (45%)	NS
Obesity	15 (18%)	10 (17%)	5 (23%)	NS
Metabolic syndrome	24 (29%)	15 (25%)	9 (41%)	NS
Hypertension	39 (48%)	26 (43%)	13 (59%)	NS

**Table 2.** Clinical and anthropometric data of the 82 patients according to the presence or absence of insulin resistance (IR)

Variables	Mean (SD)	Min-Max	IR absent	IR present	P
Age (years)	50.7 (12,1)	23 – 79	49.7 (12,3)	56.9 (10,1)	0.03
Abd. circ. (cm)	89.7 (10,7)	59 – 124	87.1 (11,1)	97.8 (11,9)	0.04
Weight (kg)	69.9 (12,6)	40.3 – 108	68.9 (11,7)	72.7 (14,7)	NS
Height (meters)	1.64 (0,1)	1.44 – 1.87	1.65 (0,1)	1.61 (0,1)	NS
BMI (Kg/m <sup>2</sup> )	26.1 (4,3)	17.7 – 40.5	25.4 (4,1)	28.1 (4,4)	0.01
SBP (mmHg)	133.1 (19,6)	100-180	128 (16,9)	131.1 (20,9)	NS
DBP (mmHg)	85.2 (12,3)	60-120	85 (11,6)	85.7 (14,5)	NS

Abd. circ.: abdominal circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure.

**Table 3.** Laboratory data of the 82 patients according to the presence or absence of insulin resistance (IR)

Variables	Mean (SD)	Min-Max	IR absent	IR Present	P
Fasting glucose	92.1 (12,9)	74-122	87.6 (10,5)	96.8 (12,8)	0.004
Fasting insulin	8.6 (7,0)	0-38.9	5.4 (3,1)	18.1 (7,1)	< 0.0001
HOMA-IR*	1.5 (1,9)	0-10.9	1.1 (0,7)	4.4 (2,0)	< 0.0001
Triglycerides	108.3 (58,6)	28-385	118.5 (71,3)	118.7 (53,4)	NS
Total cholesterol	172.8 (37,7)	77-259	179.6 (31,2)	178 (41,2)	NS
HDL-cholesterol	47.9 (14)	21-82	47.5 (14)	43.1 (10,7)	NS
PCR	0.29 (1,3)	0.1-6.6	0.6 (0,8)	1.1 (2,1)	NS
Ferritin	146.5 (168,6)	18.5-1000	167.9 (136,3)	199.8 (194,3)	NS
ALT (x URV)*	1.6 (1,6)	0.2-9.1	1.5 (0,7)	3.0 (2,3)	0.03
AST (x URV)	1.6 (0,9)	0.3-4.7	1.2 (0,6)	2.5 (1,4)	< 0.0001
GGT (x URV)*	1.0 (1,4)	0.1-8.1	1.2 (1,4)	1.4 (0,8)	0.03
Albumin	4.2 (0,5)	3.3-5.7	4.3 (0,4)	4.0 (0,6)	0.003
INR*	1.1 (0,3)	1-3.4	1.1 (0,1)	1.2 (0,2)	0.02
Platelets (x1000)	205 (79,9)	71-418	209.8 (72,2)	171.7 (54,0)	NS
Viral load (UI/mL)**	2,377,519	256-37,200,000	2,480,319	2,118,353	NS
Genotype 1	61 (77%)		46 (81%)	15 (68%)	NS

\* Mann Whitney; xURV: times the upper reference value; \*\* performed in 74 patients.

**Table 4.** Histological data of the 80 patients according to the presence or absence of insulin resistance (IR)

Variables	IR absent	IR present	P
Steatosis*	33 (42%)	19 (32%)	0.001
Liver cirrhosis***	09 (11%)	4 (44%)	NS
Fibrosis (mean $\pm$ SD)**	1.34 (1.33)	1.1 (1.2)	0.005
Fibrosis $\geq$ 2*	29 (36%)	16 (27%)	0.004
PPA (mean $\pm$ SD)**	1.49 (0.8)	1.4 (0.8)	0.04
PPA $\geq$ 2*	36 (46%)	24 (41%)	0.08

\* Chi-square; \*\* t test; PPA: periportal necroinflammatory activity; \*\*\* liver cirrhosis (2 patients did not undergo liver biopsy).

## DISCUSSION

Epidemiological studies support an association between chronic HCV hepatitis and type DM2 as the primary predisposing factor being insulin resistant (IR) (24-27). According to Mehta and cols. (2000), subjects who are more than 40 years old and have anti-HCV antibodies have a 3.77 fold higher risk of developing DM2, compared with those who were anti-HCV negative, matched for gender, BMI and ethnic background (27). Although liver cirrhosis (regardless of etiology) has been associated with the development of IR and DM2, chronic HCV infection is reported to be more strongly related with the development of IR than chronic HBV hepatitis (26).

In our study, from 82 patients, 22 (27%) had serum HOMA-IR levels greater than 2.5, which is consistent with IR diagnosis. There is no consensus on IR assessment and reference values among HCV carriers or even among subjects without liver disease. Serum HOMA-IR has been used as an indirect way to measure IR, and correlates well with insulin sensitivity using the euglycemic/hyperinsulinemic clamping technique (28,29). Cutoff points indicator of IR range from 1.5 to 3.0 (30-34) in these studies. In a 2009 Brazilian study, Geloneze and cols. analyzed 1,203 patients without diabetes and without HCV infection (35). They reported a HOMA-IR cutoff point of 2.7 for IR diagnosis, which is close to the level we used in our study. In 2008, Moucari and cols. used a HOMA-IR cutoff point of  $> 3$  to diagnose IR and found a 32% rate in 462 non-diabetic, HCV-positive patients (31).

In our study, IR was associated with age, abdominal circumference and BMI. It is known that age, obesity (particularly centripetal obesity), sedentary lifestyle and genetic predisposition are the main causes of IR in the general population (36). Advanced age is associated with lower intracellular concentrations of glucose

carriers, which are responsible for glucose entry in the cells, especially GLUT4, one of the main insulin-mediated glucose uptake regulators (36). Adipose tissue is no longer considered to be merely a lipid storage compartment, but an endocrine organ, which can secrete interleukin 6, leptin, adiponectin, insulin-like growth factor (IGF-1), and other substances that may alter insulin sensitivity (37).

In our sample, IR patients had higher levels of blood glucose, fasting insulin and HOMA-IR. Disordered glucose metabolism is certainly the main consequence of IR, supporting the higher prevalence rates of DM2 in patients with chronic hepatitis C. The levels of total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides were similar in both groups. The levels of ALT, AST and GGT were significantly higher in IR patients, which may reflect more severe inflammatory injury and the presence of steatosis. IR patients have a greater production of inflammatory cytokines, such as IL-6, resistin, TNF- $\alpha$  and CRP, which may promote inflammatory injury to the hepatocytes. Furthermore, adiponectin is a potent anti-inflammatory cytokine, and IR patients typically have lower levels of this cytokine. In this study, we found a higher rate of liver steatosis in IR patients, which may also explain the higher levels of ALT and AST. Higher levels of GGT have been observed in subjects with hyperinsulinemia, central obesity and hypertension (38). The lower levels of albumin and the increased INR in our study likely represent the higher stage of liver fibrosis observed in this group, and the consequent impairment of liver synthetic activity.

We found a significantly higher rate of hepatic steatosis in patients with IR (74%) than in those without IR (32%), a statistically significant difference. IR and obesity are likely to activate a cascade of events leading to excessive release of free fatty acids from the liver. When plasma uptake and "de novo" synthesis of free fatty acids overcome hepatocyte ability to oxidize and export these compounds as triglycerides, they accumulate in the liver parenchyma, causing steatosis (39). In this study, we observed that IR patients had higher levels of HCV-induced liver fibrosis, compared with subjects without IR. Several international studies have found similar results (8,10,31). Liver steatosis may have contributed to this finding. Steatosis could facilitate the development of liver fibrosis by means of oxidative stress resulting from the build-up of lipids in the hepatocytes, leading to greater secretion of inflammatory cytokines, formation of oxygen reactive species, and activation of liver

stellate cells, fundamental to the initiation of liver fibrogenesis (40,41). In this study, mean necroinflammatory activity was higher in IR patients. Again, liver steatosis may account for this finding.

In conclusion, this study demonstrated that 27% of non-diabetic, HCV-positive patients who were treatment-naïve, had insulin resistance, defined by serum HOMA-IR levels > 2.5, associated with age, BMI and abdominal circumference. We believe this is the first Brazilian study that demonstrates that the occurrence of IR in chronic hepatitis C patients is associated with higher inflammatory activity (biochemical and histological), advanced liver fibrosis and liver steatosis. Our data corroborates information already published for European and North American populations. IR, a potentially modifiable host-related factor, accelerates liver fibrogenesis. Future studies are needed to assess whether this strategy is able to reduce HCV-induced histological injury when metabolic parameters (IR) in HCV-positive patients are normalized.

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