

# INSULIN RESISTANCE IN PATIENTS WITH CHRONIC HEPATITIS C

Angelica Sink

## REZUMAT

**Introducere:** Insulinorezistența (IR) este factorul major în determinarea sindromului metabolic, fiind rezultatul alterării insulinosecreției și/sau insulinosensibilității. Creșterea IR în hepatita cronică C este un factor important în relația cu diabetul zaharat tip 2, cu steatoza hepatică, cu progresia fibrozei și cu non-răspunsul la tratamentul antiviral (Peginterferon și Ribavirină). **Scop:** Evaluarea IR la pacienții cu hepatită cronică C cu sau fără diabet, în comparație cu subiecții sănătoși. **Material și metodă:** Studiul s-a efectuat pe 3 loturi de pacienți, respectiv: lotul 1 - 17 pacienți cu hepatită cronică C și normoglicemie; lotul 2 - 15 pacienți sănătoși (lot martor); lotul 3 - 13 pacienți cu hepatită cronică C și diabet zaharat tip 2. La toți pacienții s-a calculat scorul HOMA-IR (Homeostasis Model Assessment for Insulin Resistance). **Rezultate:** În lotul 1 de pacienți nediabeteici cu hepatită cronică C, din cei 17 pacienți, la 8 (47%) HOMA-IR  $\geq 2$ , iar la 9 (53%) HOMA-IR  $< 2$ . În lotul 2, din cei 15 pacienți, HOMA-IR  $< 2$  la 9 pacienți (60%) și  $\geq 2$  la 6 pacienți (40%). În lotul 3 (13 pacienți), HOMA-IR  $< 2$  la 1 pacient (8%) și HOMA-IR  $\geq 2$  la 12 pacienți (92%). **Concluzii:** IR măsurată prin HOMA-IR, a fost crescută la pacienții cu hepatită cronică C nondiabeteici (47%), dar mai ales la pacienții cu hepatită cronică C diabeteici (92%), comparativ cu lotul martor ( $p = 0,0043$ ), putând fi considerată un indicator de apariție a diabetului zaharat.

**Cuvinte cheie:** hepatită cronică C, insulinorezistență, diabet zaharat tip 2, HOMA-IR

## ABSTRACT

**Introduction:** Insulin resistance (IR) represents the key feature of the metabolic syndrome, and is the result of the modification of the insulin secretion and/or of sensitivity to insulin. Increased IR in chronic hepatitis C is an important factor in relation to the type 2 diabetes, to hepatic steatosis, to the progression of fibrosis and to a non-response to the antiviral treatment (Peginterferon and Ribavirin). **Aim:** To assess IR in patients with chronic C hepatitis with or without diabetes mellitus, in comparison with normal subjects. **Material and method:** The study has been carried out on 3 groups of patients: the 1<sup>st</sup> group - 17 patients with normal glucose tolerance and with chronic hepatitis C; the 2<sup>nd</sup> group - 15 healthy patients (control group); the 3<sup>rd</sup> group - 13 patients with chronic hepatitis C and type 2 diabetes. HOMA-IR (Homeostasis Model Assessment for Insulin Resistance) was calculated in all patient groups. **Results:** In the first group (17 subjects), HOMA-IR was normal in 9 patients (53%) and increased in 8 (47%). In the second group (15 subjects), HOMA-IR was  $< 2$  in 9 subjects (60%) and  $\geq 2$  in 6 patients (40%). In the third group (13 patients), HOMA-IR  $< 2$  in 1 patient (8%) and  $\geq 2$  in 12 patients (92%). **Conclusions:** IR in patients with chronic hepatitis C, as measured by HOMA-IR, is highest in nondiabetic patients with chronic hepatitis C (47%), but especially in diabetic patients with chronic hepatitis C (92%), if compared to the control group ( $p = 0.0043$ ). Consequently, it can be considered an indicator for the occurrence of diabetes mellitus.

**Key Words:** Chronic hepatitis C, insulin resistance, type 2 diabetes, HOMA-IR

## INTRODUCTION

Insulin resistance (IR) represents the major factor underlying the metabolic syndrome, being the result of the modification of the insulin secretion and/or of sensitivity to insulin.

IR and type 2 diabetes mellitus (DM) are found more often in chronic hepatitis C compared to chronic hepatitis B. Increased IR in chronic hepatitis C is an important factor in relation to hepatic steatosis, to the progression of fibrosis and to a non-response to the antiviral treatment (Peginterferon and Ribavirin).<sup>1</sup>

IR brings on severe modifications in liver, endothelium, kidneys and is considered the central element of the metabolic syndrome, a cluster of pathological conditions consisting of abdominal obesity, abnormal glucose tolerance (impaired glucose tolerance, DM), hypertension and dyslipidemia (hypertriglyceridemia), prothrombosis and pro-inflammatory states. The components of the metabolic syndrome are universally recognized cardiovascular risk factors and are associated with an increased cardiovascular morbidity and mortality.

Department of Internal Medicine, Emergency Hospital, Petrosani

Correspondence to:

Dr. Angelica Sink, Emergency Hospital, 1 Decembrie 1918 Str., No. 137A, Petrosani, Tel: +40-254-543318  
Email: sink\_angelica@yahoo.com

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A patient with chronic hepatitis C can present two types of insulin resistance (IR): metabolic IR and viral induced IR.

The mechanism through which HCV (hepatic C virus) induces IR and the risk for the development of the type 2 DM is not fully known.

Progressive fibrosis is recognized as a factor that induces IR and type 2 DM in patients with advanced chronic hepatic disease. There are studies showing that the prevalence of type 2 DM in chronic hepatitis C with associated cirrhosis is 27%, compared to 17% in chronic hepatitis C alone. IR in hepatic cirrhosis is determined by the diminished extraction of insulin due to a hepatic cellular dysfunction and not due pancreatic hypersecretion.

The pancreas secretes equal quantities of C-Peptide and insulin; 50% of the insulin is degraded by the liver at its first passage, while C-Peptide is degraded by kidneys. By a simultaneous determination of C-Peptide and insulin in the blood serum, it has been shown that both the increased IR and the secretion of insulin determine an intolerance to glucose in patients with chronic hepatitis C. Additionally, it has been demonstrated that IR correlates even with mild hepatic fibrosis (stages  $F_0$  and  $F_1$ ) in patients with hepatitis C, compared to the healthy population or to the patients with chronic hepatitis B.<sup>2</sup>

HCV induces IR independently of BMI (body mass index) or of fibrosis stage. The mechanism by which both IR and DM are induced in patients with chronic hepatitis C has been outlined from animal studies. It seems that core protein of HCV increases the synthesis of TNF- $\alpha$ , which, at its turn, produces cytokines SOCS3 that inhibit the insulin receptors 1 and 2 (cytokines of phosphorylation), the result being a diminution of the intracellular signal at insulin with the blockage of enzyme GLUT4. GLUT4 is responsible for the access of glucose inside the cell and its blockage directly results into an increased glucose concentration in the blood.<sup>3-5</sup>

Patients with chronic hepatitis C and increased TNF- $\alpha$  levels display a high risk of DM, with severe fibrosis and low response to interferon.

Hepatic steatosis represents a modification that occurs frequently in chronic hepatitis C, being determined by the virus (genotype 3), or by a metabolic cause in genotype 1. For those with genotype 3, steatosis directly correlates with viremia. In genotype 1, steatosis directly correlates with the increase of leptin and of IR. In chronic hepatitis C, IR is associated with the progression of fibrosis (there are studies which show that hyperglycemia in these patients determines

an increased rate of progression of fibrosis, compared to the patients with normal glycemia). Starting from this aspect, Sud et al. propose an index for prediction of fibrosis at patients with chronic hepatitis C, by taking into consideration the following parameters: age, cholesterol level,  $\gamma$ -GT, consumption of alcohol, and HOMA-IR.<sup>6-8</sup>

The mechanisms by which IR determines the progression of fibrosis are steatosis, hyperleptinemia, increased TNF- $\alpha$  levels, a diminution of the PPAR $\gamma$  receptors (peroxisome proliferator activated receptor gamma).

Leptin produces a direct stimulation of stellate cells, with an increase in the synthesis of collagen and its arrangement into a matrix. TNF- $\alpha$  stimulates the stellate cells and diminishes the activity of PPAR $\gamma$ . The patients with hepatitis C display a diminution of PPAR $\gamma$  receptors, thus resulting that agonists PPAR $\gamma$  would block the inflammation and progress of fibrosis by blocking the transcription of factor NF $\kappa$ B and of TGF- $\beta$ 1.<sup>9,10</sup>

The response of the patients with hepatitis C to the antiviral treatment was studied taking into consideration IR. The response to antiviral therapy depends on a series of factors, such as: genotype, viremia, HLA, weight, steatosis, age, fibrosis, and race. Some studies have showed that the answer to the treatment is independently associated with BMI, obesity, steatosis, and fibrosis.<sup>6</sup>

IR can best be determined by the euglycemic clamp method, but the current practice uses a mathematical model, i.e. HOMA (HOMEOSTASIS MODEL ASSESSMENT) which correlates intimately with the euglycemic clamp method ( $r = 0.820$ ). The method is limited, i.e. it provides correct data as long as the glucose level is near to normal, being less efficient in subjects with DM, with clinical manifestations. HOMA model consists in a number of non-linear equations that predict the concentration of fasting glucose and of insulin for any combination between the cellular function  $\beta$  and the resistance to insulin. The cellular function  $\beta$  (%) and sensitiveness (%S) can be estimated based on this prediction by measuring fasting glucose and insulin levels. Resistance to insulin (%R) is the reverse of sensitiveness (1/S) and can be calculated with the help of the following equation:

$$\%R = I \times G / 22.5$$

Where I is the basal insulinemia ( $\mu$ U/ml), G is the basal plasma glucose (mmol/l).

When G is expressed in mg/dl, then the figure

of the denominator changes from 22.5 to 405, more exactly:  $\%R = I \times G / 405$ .

There is no standard value for HOMA-IR. The current studies consider that HOMA-IR < 2 is normal, HOMA-IR ≥ 2 is pathological, with HOMA-IR > 4 reflecting the pre-diabetic stage.<sup>4</sup>

## MATERIAL AND METHODS

The study was carried out on three groups of patients:

- 1<sup>st</sup> group consisted of 17 normoglycemic patients with chronic hepatitis C that came in for a check up in February 2007 at Emergency Hospital in Petrosani, Department of Internal Medicine, 9 women and 8 men aged between 39 and 80 (average age: 59 years);

- 2<sup>nd</sup> group (control) comprised 15 healthy subjects, 9 women and 6 men aged between 27 and 55 (average age: 58 years);

- 3<sup>rd</sup> group consisted of 13 patients with chronic hepatitis C and type 2DM, with blood glucose levels below 250 mg/dl; these patients came for a check up in February 2007 at Emergency Hospital Petrosani, Department of Internal Medicine; there were 10 women and 3 men aged between 51 and 75 (average age of 67 years).

The diagnostic of chronic hepatitis C was determined based on the clinical, biological and histological criteria.

DM was diagnosed by fasting plasma glucose equal to or greater than 126 mg/dl or by 2h-glucose during an OGTT equal to or greater than 200 mg/dl. HOMA-IR was assessed by determining the basal glucose (mg/dl) and basal insulinemia (μU/ml) with the analyzer IMMULITE 1000 and it was calculated with the following equation:  $\% R = I \times G / 405$ , where I is the basal insulinemia (μU/ml), G is the basal plasma glucose (mg/dl). Interpretation of HOMA-IR was performed as follows: < 2: normal value; ≥ 2: pathological value; > 4: pre-diabetic stage.

## RESULTS

The results are shown in the Tables 1, 2 and 3.

**Table 1.** HOMA-IR in non-diabetic patients with chronic hepatitis C.

n	17
women / men	9/8
Average age, yrs	59
HOMA-IR < 2, n, %	9 (53%)
HOMA-IR ≥ 2, n, %	8 (47%)

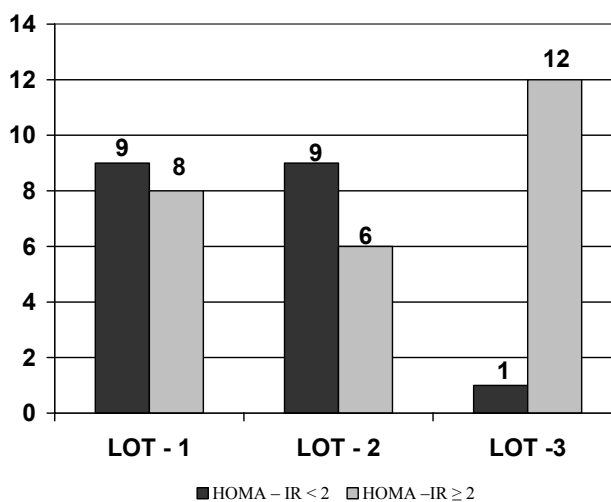
**Table 2.** HOMA-IR in healthy subjects (control group).

n	15
women / men	9/6
Average age, yrs	58
HOMA-IR < 2, n, %	9 (60%)
HOMA-IR ≥ 2, n, %	6 (40%)

**Table 3.** HOMA-IR in patients with chronic hepatitis C and DM.

n	13
women / men	10/3
Average age, yrs	67
HOMA-IR < 2, n, %	1 (8%)
HOMA-IR ≥ 2, n, %	12 (92%)

The number of subjects with HOMA-IR ≥ 2 in the three study groups is shown in Figure 1.



**Figure 1.** HOMA-IR in the three study groups

## DISCUSSIONS

One can notice that a HOMA-IR ≥ 2 was found in the first group (non-diabetic patients with chronic hepatitis C) in 47% of the cases, slightly higher compared to the control group (where HOMA-IR ≥ 2 was found in 40% of the cases).

The range for abnormal values of HOMA-IR was 2 to 10 in the 1st group and 2 to 7 in the second group (controls).

HOMA-IR ≥ 4 (prediabetic stage) was found in four patients (23.5%) from the first group and in three controls (20%).

Values of HOMA-IR ≥ 2 were found in an important percent (40%) of cases from the second group (controls), but we have not taken into account other factors that could determine IR.

In the third group (patients with chronic hepatitis

C and type 2 DM), HOMA-IR values are  $\geq 2$  in 92% of patients, as we expected. Nevertheless, it has to be underlined the fact that the mathematic model HOMA allows a correct estimation for glucose level near to normal. A value of HOMA-IR  $\geq 2$  was also found in patients treated with insulin, so it is necessary to add certain drugs (biguanides, pioglitazone) which reduce IR and consequently its hepatic effects.

The results obtained by the present study can also be found in the literature, to the extent to which they show that patients with chronic hepatitis C exhibit an increased IR (measured by HOMA-IR), responsible for intolerance to glucose. Even if there is not a big difference between HOMA-IR in the non-diabetic patients with chronic hepatitis C and that obtained in the control group, our study confirms that patients with chronic hepatitis C present a modification in insulin sensitivity, i.e. a diminution of sensitiveness, with a risk of occurrence of type 2 DM, especially in those subjects with HOMA-IR  $\geq 4$ .

Determination of HOMA-IR in patients with chronic hepatitis C could help to predict the development of DM that requires therapy. Thus, patients may be given drugs that decrease their IR before the onset of type 2 DM with clinical manifestations, therefore reducing the risk of DM progression as well as that of the progress of the hepatic disease towards cirrhosis.

An increased HOMA-IR in the patients with chronic hepatitis C and euglycemia can contribute to the following:<sup>11-16</sup>

- Development of metabolic syndrome, together with other factors (increased BMI) with the well-known cardiovascular risk;
- Hepatic steatosis, especially in genotype 1 infections, prevailing in Romania;
- Development and progression of fibrosis by a direct stimulation of stellate cells of the liver;
- A decreased response to antiviral treatment; the current studies show that the values of HOMA-IR fall below 2 in the responders, suffers no change in the non-responders and at increase with the increment of viremia in the patients with no steady viral response.

In the third group of patients (patients with chronic hepatitis C and type 2 diabetes), HOMA-IR values range between 2 and 40, compared to healthy patients or to those with normal glucose and chronic hepatitis C. Thus, for this group of patients it is necessary to reduce IR, and this would allow both an improved metabolic control and a diminution of hepatic consequences of the increased IR.

Determination of IR by measuring HOMA-IR at

the patients with chronic hepatitis C, but with normal glucose tolerance, could represent an important indicator in assessing risk, in concert with other criteria. In addition, in patients with hepatitis C and increased HOMA-IR, the use of drugs that reduce IR could contribute to a steady therapeutic response and could reduce the incident type 2 DM cases. An on-going study (TRIC-1) has randomized patients with chronic hepatitis C, genotype 1, and increased HOMA-IR treated with Peginterferon  $\alpha_{2a}$  and Ribavirin to either Metformin or placebo.<sup>11</sup>

The results of the present study cannot be generalized since it used a small group of patients, but they are concordant with the results of other studies on IR in the patients with chronic hepatitis C.

## CONCLUSIONS

IR in patients with chronic hepatitis C determined by HOMA-IR reaches high values in non-diabetic patients with chronic hepatitis C (47%), but especially in diabetic patients with chronic hepatitis C (92%), compared to the control group ( $p=0.0043$ ); consequently, it can be considered an indicator for the occurrence of DM.

Considering the results of the present study, the determination of IR by HOMA-IR in patients with chronic hepatitis C could predict, especially when values are  $\geq 4$ , the risk of occurrence of DM and a weak response to antiviral therapy.<sup>6</sup>

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