

Insulin resistance reduction after sustained virological response with direct acting antiviral: not every population improves

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ABSTRACT – Background – Hepatitis C virus (HCV) infection is a serious public health problem, that affects approximately 170 million people worldwide. Chronic HCV infection is associated with hepatic insulin resistance and an increased risk of diabetes HCV-infected patients has been well documented. **Objective** – To assess the homeostasis model assessment of insulin resistance (HOMA-IR) index in patients treated with direct acting antiviral (DAAs) medication in the sustained virological response (SVR), categorized by the presence or absence of cirrhosis. **Methods** – A prospective study was conducted. Data were collected at the beginning of treatment (t-base) and in the twelfth week after the completion of treatment (t-SVR12). The inclusion criteria were presence of: HCV infection (RNA-HCV positive), age ≥ 18 years, completion of DAAs' therapy, and presence of diabetes with use of oral hypoglycemic agents. All samples were collected during the study period. The exclusion criteria were: presence of HBV/HIV co-infection, hepatocellular carcinoma at baseline, diabetic patients taking insulin and transplanted patients (liver/kidney). Fibrosis was assessed by hepatic elastography or biopsy (METAVIR). Cirrhosis was determined by clinical results or imaging. HOMA-IR was calculated as fasting insulin ($\mu\text{U/mL}$) \times fasting glucose (mmol/L)/22.5. The patients were divided into two groups: the general study population (all patients, including the diabetic patients) and the special population (patients with normal values of HOMA-IR, which is >2.5 , and without diabetes). The delta HOMA-IR value was calculated as: HOMA-IR at t-base – HOMA-IR at t-SVR12. For the descriptive statistical analysis, the paired t-test and generalized linear model assuming the log binding function were performed. A *P* value of < 0.05 was considered significant. **Results** – We included 150 patients, and 75 were cirrhotic. The mean age was 55.3 ± 9.97 and body mass index was 27.4 ± 5.18 . Twenty-two (14.67%) were diabetic patients using oral hypoglycemic agents, and 17 (11%) were cirrhotic. In the general study population, the mean glucose and HOMA-IR values increased at t-SVR12, but insulin decreased. Delta HOMA-IR was negative at t-SVR12, but there was no significant difference. Excluding diabetic patients and those with normal HOMA-IR values (<2.5), mean glucose, insulin and HOMA-IR decreased at t-SVR12. Delta HOMA-IR decreased significantly at t-SVR12 (*P*: 0.02). **Conclusion** – In the general population, glucose and HOMA-IR values increased at t-SVR12, but insulin decreased. In the special population, glucose, insulin, HOMA-IR and Delta HOMA-IR decreased at t-SVR12.

HEADINGS – Hepatitis C. Insulin resistance. Antiviral agents.

INTRODUCTION

Hepatitis C virus (HCV) infection is a serious public health problem, that affects approximately 170 million people worldwide⁽¹⁾. It continues to be the leading cause of death from liver disease and, despite recent medical advances in HCV therapy, it is the principal indication for liver transplantation in the United States^(2,3). Eighty-five percent of the infected people fail to achieve clearance of the virus and become chronically infected⁽⁴⁾. Approximately 20% may develop hepatic cirrhosis within 20 years, characterized by progressive replacement of the functional hepatic architecture by non-functional fibrotic tissue. Each year, 6% of cirrhotic patients are expected develop terminal hepatic disease, and 4% to develop hepatocellular carcinoma (HCC)^(5,6).

Chronic HCV infection is associated with hepatic insulin resistance (IR) and an increased risk of diabetes in HCV-infected patients has been well described⁽⁷⁾. This large prevalence of type

2 diabetes (T2DM) in HCV remains even when cirrhotic patients are excluded from the analysis⁽⁸⁻¹⁰⁾, indicating that cirrhosis could be diabetogenic by itself⁽¹¹⁾. Although insulin resistance (IR) has also been detected also in subjects with minimal or no fibrosis, an increase of homeostatic model assessment of insulin resistance (HOMA-IR) has been associated with the presence of more advanced fibrosis⁽¹²⁾. Other studies confirmed these findings and showed a correlation between the degree of fibrosis and IR^(13,14). T2DM and IR were observed to be independent predictors of liver-related mortality^(15,16), moreover IR was associated with fibrosis progression and the stage of fibrosis⁽¹²⁾.

In patients receiving interferon (IFN)-based therapy, Romero-Gomez et al.⁽¹⁷⁾ showed that IR was associated with lower sustained virological response (SVR) rates, independent of a viral genotype. Baseline IR did not affect the outcomes of direct acting antiviral (DAA) -based therapy and HOMA-IR scores had no effect on virological response to interferon free therapy^(18,19).

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IFN based therapy improved the IR in SVR⁽²⁰⁾, however, it is unclear if this effect occurs during direct acting antiviral therapy. Thus, our aim was to assess HOMA-IR behavior in patients treated with DAAs that reached the SVR, categorized by the presence or absence of cirrhosis.

METHODS

In this prospective study, we assessed patients treated with interferon free therapy from 2015 to 2017. The study was conducted at the Viral Hepatitis Outpatient Clinic of Botucatu Medical School and was approved by the Committee on Ethics in Research of the Botucatu Medical School. The data were collected at the beginning of treatment (baseline: t-base) and in the twelfth week after treatment was completed (t-SVR12).

The inclusion criteria were: presence of chronic hepatitis C infection (presence of RNA-HCV); age ≥ 18 years; completion of DAAs' therapy; presence of diabetes with intake of oral hypoglycemic agents, and samples collected during the study period. The exclusion criteria were as follows: HBV and/or HIV co-infection; hepatocellular carcinoma at baseline; diabetic patients taking insulin and transplanted patients (liver and kidney).

Fibrosis was assessed by hepatic elastography or biopsy (METAVIR classification)⁽²¹⁾. Cirrhosis was determined clinically or by imaging examination. HOMA-IR was calculated as fasting insulin ($\mu\text{U/mL}$) \times fasting glucose (mmol/L)/22.5⁽²²⁾. To determine the delta HOMA-IR value, the difference was calculated as the HOMA-IR at t-base – HOMA-IR at t-SVR12.

Descriptive statistical analyses were performed to establish a comparison of the delta HOMA-IR between the groups: the general study population (all patients, including diabetics patients) and the special population (We excluded patients with normal values of HOMA-IR, which is < 2.5 , and with diabetes). For delta HOMA-IR, delta insulin and delta glucose, the paired t test was performed. A generalized linear model assuming log-binding function was performed for delta HOMA-IR evaluated by fibrosis. A *P*-value of < 0.05 was considered significant.

RESULTS

Of the 274 consecutive patients, 150 were included, and 75 were cirrhotic. Six patients died during the treatment period, 15 were excluded for taking insulin, 10 did not achieve SVR, 3 had a hepatic nodule at baseline, 7 underwent kidney or liver transplantation and 83 did not have data for HOMA-IR in all the periods indicated.

The mean age was 55.3 ± 9.97 and body mass index (BMI) was 27.4 ± 5.18 . Twenty-two (14.67%) were diabetic patients who required oral hypoglycemic agents, and 17 (11%) were cirrhotic ($P=0.01$).

In TABLE 1 the baseline results of the general study population are provided. Mean glucose and HOMA-IR increased at t-SVR12 (102.36 ± 24.52 and 3.72 ± 3.26 respectively), but insulin decreased (14.03 ± 10.32).

In TABLE 2 the changes in of delta glucose, delta insulin and delta HOMA-IR values are provided.

Although the delta HOMA-IR was negative at t-SVR12, there was no statistical difference. When we evaluated the delta HOMA-IR based on the presence of advanced fibrosis or not, no statistical difference was found either. ($P=0.58$).

TABLE 1. Baseline results in the general population.

	t-base (n=150)
Age	55.3 \pm 9.97
BMI	27.4 \pm 5.18
F \leq 2 / F3 / F4(%)	54(36%) / 21(14%) / 75(50%)
Diabetics taking oral hypoglycemic agents	14.67% / F \leq 3 (3%) / F4 (11%)
Glucose	100.65 \pm 19.7
Insulin	14.46 \pm 10.26
HOMA-IR	3.69 \pm 2.99

t-base: baseline; BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance.

TABLE 2. Values of delta glucose, delta insulin and delta HOMA-IR in the general population.

	Mean delta (n=150)	<i>P</i> -value
Delta glucose	-1.71 \pm 15.61	0.18
Delta insulin	0.48 \pm 8.82	0.5
Delta HOMA-IR	-0.009 \pm 2.66	0.96

Delta: t-base–t-SVR; HOMA-IR: homeostasis model assessment of insulin resistance; t-base: baseline; t-SVR12: sustained virological response.

Analyses of special population – when we excluded patients with normal values of HOMA-IR, which is < 2.5 and with diabetes.

Excluding diabetic patients and those who had normal HOMA-IR values (HOMA-IR < 2.5) there were 75 patients in total, 21 (28%) were F \leq 2, 12 (16%) were F3 and 42 (56%) were F4 (TABLE3).

In this population, the mean glucose, insulin and HOMA-IR values decreased at t-SVR12 (98.25 ± 14.58 , 16.56 ± 7.64 , 4.09 ± 2.13), respectively.

TABLE 3. Baseline results in the population without diabetic patients and normal values of HOMA-IR TW0.

	t-base (n=75)
Age	55.98 \pm 9.47
BMI	28.66 \pm 5.18
F \leq 2 / F3 / F4(%)	21(28%) / 12(16%) / 42(56%)
Glucose	100.85 \pm 15.09
Insulin	19.46 \pm 8.92
HOMA-IR	4.86 \pm 2.44

t-base: baseline; BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance.

In TABLE 4 delta glucose, delta insulin and delta HOMA-IR are provided after excluding diabetic patients and those who had normal values of HOMA-IR (< 2.5). The Delta HOMA-IR decreased significantly at t-SVR12. When categorized by fibrosis, there was no statistical difference ($P=0.98$).

TABLE 4. Values of delta glucose, delta insulin and delta HOMA-IR in patients with values of HOMA-IR > 2.5 and non-diabetics.

	Mean delta (n=75)	<i>P</i> -value
Delta glucose	2.6 \pm 12.49	0.07
Delta insulin	2.9 \pm 9.88	0.01
Delta HOMA-IR	0.76 \pm 2.81	0.02

Delta: t-base–t-SVR; HOMA-IR: homeostasis model assessment of insulin resistance; t-base: baseline; t-SVR: sustained virological response.

DISCUSSION

Numerous studies suggest that HCV can harm insulin signaling and increase the onset of T2DM^(23,24). In HCV-infected patients the reported prevalence of IR has increased from 30% to 70%, irrespective of the severity of hepatic disease, and is genotype-specific^(2,15). In our study, the incidence of T2DM was 14.6%, and 11% of patients were cirrhotic and 3.33% were non cirrhotic ($P < 0.01$).

Diabetes mellitus caused by cirrhosis is called hepatogenous diabetes. This type of diabetes is most likely caused by IR with a lower hepatic extraction of insulin or by some dysfunction of pancreatic beta cells; however, this mechanism is not completely understood⁽²⁵⁾. Classification of patients according to hepatogenous diabetes or hereditary T2DM to better determine the effect of HCV eradication in these conditions, would be beneficial⁽²⁶⁾. However, this is not always possible because there is no standard definition of hepatogenous diabetes, even in international guidelines.

The impact of IR on the treatment efficacy of DAAs has greatly reduced because of the recent development of high potency antivirals⁽¹⁶⁾. However, post-treatment outcomes with respect to glucose abnormalities have rarely been investigated. Thus, the correlation and/or changes of IR with treatment efficacy of DAAs in a real-world scenario needs more assessment.

Our data showed that the delta HOMA-IR increased at SVR12, but the result was not statistically significant, when the general study population, including diabetic patients, were studied. Additionally, there was no association between HOMA-IR and low and high levels of fibrosis. In this population, there was a slight increase of glucose and HOMA-IR, while the insulin levels decreased. A study by Jeef-Fu Huang et al.⁽¹⁹⁾, that included 65 native Taiwanese patients with chronic hepatitis C treated with DAAs assessing HOMA-IR, it was observed that, the levels of HOMA-IR decreased at SVR12, compared to baseline, even though there was no statistical difference. In addition, the mean glucose levels decreased in diabetic patients at SVR12. The study did not show the level of fibrosis in the patients. Another study that consisted of 110 patients with chronic hepatitis C, advanced fibrosis and T2DM that analyzed the impact of SVR on fasting glucose and glycated hemoglobin, also showed a significant reduction in fasting glucose, as SVR12 was the only factor associated with this improvement⁽²⁷⁾. However, they did not evaluate HOMA-IR.

There is no consensus regarding the cut-off value for diagnosing IR^(28,29). Some studies use a HOMA-IR value between 1.5 and 3.0 to

determine insulin resistance^(17,30-32). In our study, we used HOMA-IR > 2.5 for the diagnosis of insulin resistance. In Brazil, there was a populational study of non-diabetic patients without HCV infection from the Brazilian Study of Metabolic Syndrome⁽³²⁾. In this study the optimal diagnostic level of HOMA-IR was between 2.3 and 2.7, which is close to the level used in our study.

In our study, on excluding diabetic patients and those with a HOMA-IR < 2.5 (special population), a decrease in glucose, insulin and HOMA-IR values at t-SVR12 was observed. A study of 133 HCV genotype 1 patients with advanced liver fibrosis without T2DM⁽³³⁾ that evaluated the impact of HCV clearance by anti-viral treatments on IR and glycemic control, showed similar results to ours. Glucose, insulin and HOMA-IR values decreased at the end of treatment, resulting in values that remained constant after SVR12. The HOMA-IR values were associated with advanced liver fibrosis, however in our study, we did not find a significant association between the delta HOMA-IR and fibrosis stage. This might be attributable to the small study population of 75 patients after excluding diabetic patients and those with HOMA-IR < 2.5 .

CONCLUSION

Glucose and HOMA-IR increased at t-SVR12, but insulin decreased in the general population. The delta HOMA-IR increased, but there was no association with the stage of fibrosis. Excluding diabetic patients and those who had normal values of HOMA-IR, glucose, insulin, HOMA-IR and delta HOMA-IR decreased at t-SVR12. In addition, no association with fibrosis was found.

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Authors' contribution

Designed the study and wrote the paper: Andrade VG and Silva GF. Performed the reasearch: Yamashiro FS, Oliveira CV, Moreira A and Winckler FC. Revised the manuscript for final submission: Silva GF.

Andrade VG, Yamashiro FS, Oliveira CV, Moreira A, Winckler FC, Silva GF. Redução da resistência à insulina após resposta virológica sustentada com agentes antivirais diretos: nem toda população melhora. *Arq Gastroenterol.* 2018;55(3):274-8.

RESUMO – Contexto – A infecção pelo vírus da hepatite C (VHC) é um grave problema de saúde pública, que afeta aproximadamente 170 milhões de pessoas no mundo. A infecção crônica pelo VHC está associada à resistência à insulina hepática e a um risco aumentado de diabetes. Os doentes infectados pelo VHC foram bem documentados. **Objetivo** – Avaliar o modelo de avaliação da homeostase do índice de resistência à insulina (HOMA-IR) em pacientes tratados com medicação antiviral de ação direta na resposta virológica sustentada (RVS), categorizada pela presença ou ausência de cirrose. **Métodos** – Foi realizado um estudo prospectivo. Os dados foram coletados no início do tratamento (t-base) e na décima segunda semana após o término do tratamento (t-RVS12). Os critérios de inclusão foram presença de: infecção pelo VHC (RNA-VHC positivo), idade ≥ 18 anos, conclusão da terapia de antivirais de ação direta e presença de diabetes com uso de hipoglicemiantes orais. Todas as amostras foram coletadas durante o período do estudo. Os critérios de exclusão foram: presença de coinfeção VHB/HIV, carcinoma hepatocelular no início do estudo, pacientes diabéticos em uso de insulina e pacientes transplantados (fígado/rim). A fibrose foi avaliada por elastografia hepática ou biópsia (METAVIR). A cirrose foi determinada por resultados clínicos ou exames de imagem. O HOMA-IR foi calculado como insulinemia de jejum ($\mu\text{U/mL}$) x glicemia de jejum (mmol/L) / 22,5). Os pacientes foram divididos em dois grupos: a população geral do estudo (todos os pacientes, incluindo os diabéticos) e a população especial (pacientes com valores normais de HOMA-IR, que é $< 2,5$ e sem diabetes). O valor do delta HOMA-IR foi calculado como: HOMA-IR no t-base – HOMA-IR no t-RVS12. Para a análise estatística descritiva, foram utilizados o teste t pareado e o modelo linear generalizado, assumindo a função de ligação logarítmica. Um valor de $P < 0,05$ foi considerado significativo. **Resultados** – Foram incluídos 150 pacientes e 75 eram cirróticos. A idade média foi de $55,3 \pm 9,97$ e o índice de massa corpórea foi de $27,4 \pm 5,18$. Vinte e dois (14,67%) eram pacientes diabéticos em uso de hipoglicemiantes orais e 17 (11%) eram cirróticos. Na população geral do estudo, os valores médios de glicose e HOMA-IR aumentaram na t-SVR12, mas a insulina diminuiu. O delta HOMA-IR foi negativo em t-SVR12, mas não houve diferença significativa. Excluindo pacientes diabéticos e aqueles com valores normais de HOMA-IR ($< 2,5$), a média de glicose, insulina e HOMA-IR diminuiu no t-RVS12. O delta HOMA-IR diminuiu significativamente em t-RVS12 ($P: 0,02$). **Conclusão** – Na população geral, os valores de glicose e HOMA-IR aumentaram no t-RVS12, mas a insulina diminuiu. Na população especial, glicose, insulina, HOMA-IR e delta HOMA-IR diminuíram no t-RVS12.

DESCRIPTORIOS – Hepatite C. Resistência à insulina. antivirais.

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