

Curing hepatitis C with the new direct acting antivirals did not improve insulin resistance after one year

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ABSTRACT – Background – Chronic hepatitis C still figures as an important cause of morbidity among the Brazilian population, and is closely associated with metabolic disturbances, including insulin resistance (IR), which can be evaluated by the Homeostatic Model Assessment (HOMA-IR). IR may entail lower sustained virologic response (SVR) on certain therapeutic regimens and faster progression to advanced hepatic fibrosis. With the arrival of the direct acting agents (DAA) in hepatitis C treatment, there is an increased need in observing the impact in patients' IR profile while using such therapies. **Objective** – 1) To compare the results of HOMA-IR in patients affected by chronic hepatitis C before treatment with DAA and 12 months after finishing it with SVR. 2) To evaluate the evolution of weight after curing chronic hepatitis C. **Methods** – We included patients older than 18 from two tertiary care in Curitiba – PR, of both sexes, with chronic hepatitis C, treated with DAA, from July 2015 to September 2017. We also evaluated the patients' levels of fasting insulin, fasting glucose and glycated hemoglobin before starting treatment and 12 months after finishing it. We also used epidemiologic data, such as age, sex, hepatic fibrosis degree, body mass index, abdominal circumference, viral genotype and the presence of diabetes mellitus before and after treatment. IR was assessed before and after treatment and calculated by the HOMA-IR score. Insulin resistance was defined by a HOMA-IR greater than 2.5. We excluded patients who lost follow-up, those who did not achieve SVR and those who did not have a laboratory profile. The results of quantitative variables were described by means, medians, and standard deviations. *P* values <0.05 indicated statistical significance. **Results** – We included 75 patients in this study, with a mean age of 55.2 years and 60% of males. Forty-three patients had advanced fibrosis. Twenty one (28%) had a previous diabetes mellitus diagnosis. We identified 31 (41.3%) patients with IR before antiviral treatment, and this number increased to 39 (52%) after 12 months of finishing treatment, according to HOMA-IR. There was no statistic difference between insulin, glucose and HOMA-IR measurements before and after curing hepatitis C. We observed a weight gain in patients shortly after curing hepatitis C, but this did not persist at the end of the study. We also had no significant difference in IR prevalence when viral genotype was concerned. **Conclusion** – In this study, there was no statistically significant difference between HOMA-IR results in patients before and 12 months after treatment for hepatitis C. Even though patients gained weight after the cure, this was not statistically significant after a year (*P*=0.131).

HEADINGS – Hepatitis C. Insulin resistance. Diabetes mellitus. Antiviral agents.

INTRODUCTION

Since the discovery of the hepatitis C virus (HCV) in 1989, there has been much discussion about the association of chronic HCV infection and the development of type 2 diabetes (T2D) within the scientific community⁽¹⁾. The first observation that cirrhotic patients infected with HCV may present with T2D more often than those with cirrhosis due to other aetiologies comes from a report by Allison, Wreghitt, Palmer and Alexander^(2,3). HCV can promote insulin resistance (IR) regardless of liver disease severity through interactions with different components of the insulin signalling pathway or altering aspects involved in its regulation⁽⁴⁾ and IR is the best predictor for the development of diabetes, preceding the onset of diabetes by 10 to 20 years⁽⁵⁾.

Prevalence of HCV infection is higher in diabetic patients

when compared to the general population^(5,6,7,8,9). Furthermore, previous researches show that patients with chronic hepatitis C have a higher prevalence of T2D compared to other liver diseases and the general population, even when considering those who are not cirrhotic yet^(2,5,8,10-14).

T2D is recognized for modifying the course of hepatitis C, with studies indicating a faster progression of liver fibrosis in diabetic patients^(5,15). There is also data indicating an increased risk of hepatocellular carcinoma in patients with T2D and HCV infection^(3,16,17).

Some studies reported an improvement in IR and a reduced risk of T2D in patients who achieved sustained virologic response (SVR) after HCV treatment with interferon-based therapies^(1,4,5,18-20). Higher levels of IR were also associated with lower SVR rates in patients treated with the pegylated interferon and ribavirin^(15,21-26).

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Earlier studies postulated that the effect of HCV infection on IR depended on viral genotype, since the increased prevalence of diabetes in HCV was predominantly observed among genotype 1 and 2 infected subjects. It is of interest that, despite lower IR levels, subjects with HCV genotype 3 have more extensive hepatic steatosis. The implication that steatosis in genotype 3 is mediated predominantly by viral factors and not by IR is consistent with earlier reports^(5,12,27-30).

HCV infection and T2D are two major global epidemics responsible for high costs to healthcare and for increasing patient morbidity and mortality. This study aims to compare the level of IR of patients with chronic hepatitis C before treatment with the new direct-acting antivirals (DAAs) and up to 12 months after SVR and to evaluate the evolution of weight after curing chronic hepatitis C.

METHODS

This prospective study included 75 patients over 18 years old, of both genders, submitted to treatment with DAAs (sofosbuvir with daclatasvir, simeprevir or ledipasvir – with or without ribavirin – or the drug composed of ombitasvir, veruprevir, ritonavir and dasabuvir, with or without ribavirin), in the period from July 2015 to September 2017, in a tertiary service in the city of Curitiba, Brazil. This research was approved by the Ethics Committee of the Federal University of Paraná. Patients had blood samples collected for fasting insulin, fasting glycemia, and glycated haemoglobin prior to initiating treatment for hepatitis C and up to 12 months after the end of the treatment. Information about patients' age, gender, liver fibrosis, body mass index (BMI), abdominal circumference (AC), HCV genotype and presence of T2D was also collected. Patients taking oral hypoglycaemic agents or those meeting the criteria defined for T2D diagnosis according to the Brazilian Society of Diabetes (random glucose ≥ 200 mg/dL with typical symptoms; fasting glycemia ≥ 126 mg/dL or 2 hours post-overload of 75 g glucose ≥ 200 mg/dL) were classified as diabetics^(31,32). We excluded from the study those who lost follow-up, who did not reach SVR and those who did not have laboratory tests. Insulin resistance – estimated before and 12 months after the end of HCV treatment – was calculated by homeostatic model assessment (HOMA) using the equation:

$$\text{HOMA} = \text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose } (\text{mg/dL}) / 405.$$

According to the current literature, IR equalled to a HOMA greater than 2.5^(33,34). The results of quantitative variables were described by means, medians, and standard deviations. For categorical variables, frequencies and percentages were presented. Comparison of pre- and post-treatment moments, in relation to quantitative variables, was done using the Wilcoxon non-parametric test. Regarding insulin resistance, this comparison was made considering the binomial test. To evaluate the association between categorical variables and insulin resistance, Fisher's exact test was used. The comparison of patients with and without insulin resistance in relation to quantitative variables was done using the Student's t-test for independent samples or the non-parametric Mann-Whitney test. The variables normality condition was evaluated by the Kolmogorov-Smirnov test. Values of $P < 0.05$ indicated statistical significance. Data analysis used the Stata/SE 14.1 software.

RESULTS

Among the 75 patients included in this study, 45 (60%) had genotype 1 HCV infection, while 28 (37.4%) were genotype 3, and only 1 (1.3%) patient had HCV genotype 4. The average patient age was 55.2 years old and 60% of the individuals were male. The mean BMI was 26.4 kg/m², with 41 (55.7%) patients having BMI > 25 kg/m². As of the beginning of the study, 21 (28%) patients were already diabetic. In addition, 5 (6.7%) patients were coinfecting with the human immunodeficiency virus (HIV), and 3 (4%) underwent liver transplantation prior to treatment of chronic hepatitis C (TABLE 1).

TABLE 1. Baseline characteristics from the studied population.

Variables	Results
Age (years)	55.2 ± 10.5 (33–77)
Weight (kg)	73.5 ± 15.1 (47–108)
Male Gender	45 (60%)
BMI (kg/m ²)	26.4 ± 4.8 (17.4–44.4)
Abdominal circumference (cm)	92.5 ± 13.4 (64–121)
Hepatic fibrosis ≥ 3	43 (81.1%)
Diabetics	21 (28%)
Genotype	
1	45 (60%)
2	1 (1.3%)
3	28 (37.4%)
4	1 (1.3%)

Fifty-three patients had their hepatic fibrosis measured using laboratory scores (APRI or FIB4), hepatic elastography or liver biopsy. Forty-three (81.1%) had advanced fibrosis (METAVIR 3 or 4).

Insulin resistance was present in 31 (41.34%) patients prior to antiviral treatment, increasing to 39 (52%) according to the HOMA calculation after 12 weeks of the end of treatment. There was no statistical significance between pre and post treatment concerning IR among patients ($P = 0.077$).

There was no significant difference between insulin, fasting glucose and HOMA-IR results before and after curing chronic hepatitis C (TABLE 2 and FIGURE 1).

TABLE 2. Fasting insulin, fasting glucose and HOMA results, before and after sustained virologic response.

Variables	Mean	Median	SD	P value
Fasting insulin				
Pre-treatment	17.7	17.6	9.5	0.756
Post-treatment	17.2	14.1	12.5	
Fasting glucose				
Pre-treatment	115.5	95.5	55.4	0.280
Post-treatment	109.3	96.4	47.5	
HOMA-IR				
Pre-treatment	4.6	4.2	2.8	0.756
Post-treatment	6.3	3.4	8.3	

SD: standard deviation.

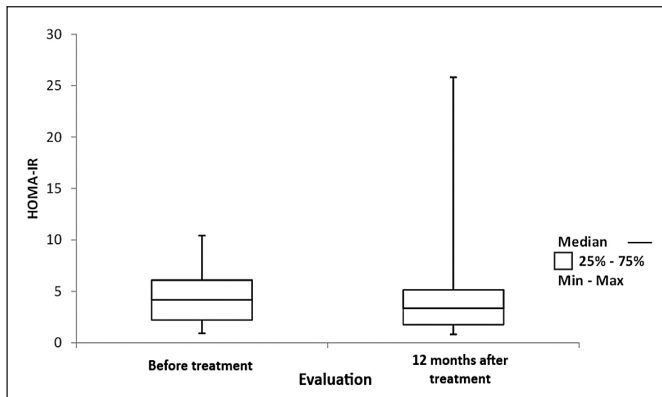


FIGURE 1. HOMA-IR variation: before treatment and after 12 months of sustained virologic response.

Regarding IR before treatment, its presence was independent of the patients' age, gender, BMI, AC value, viral load value or presence of advanced fibrosis. On the other hand, weight was directly related to IR (TABLE 3).

TABLE 3. Insulin resistance correlation with age, weight and viral load: pre and post treatment of chronic hepatitis C.

Variables	Mean	Median	Min	Max	SD	P value
Age						
Pre treatment	57.97	57	41	77	9.7	0.089
Post treatment	56.49	57	40	77	13.71	0.340
Weight						
Pre treatment	77.72	76	50	104	13.34	0.007
Post treatment	77.19	75	50	104	13.71	0.001
Viral load (log/mL)						
Pre treatment	5.72	5.96	3.83	6.97	0.78	0.525
Post treatment	5.70	5.97	2.05	6.97	0.98	0.197

SD: standard deviation.

When regarding exclusively nondiabetic patients, there was also no statistical change in the HOMA-IR results before and after SVR (TABLE 4).

TABLE 4. HOMA-IR results before treatment and after sustained virologic response, excluding diabetic patients.

Variable	Mean	Median	SD	P value
HOMA-IR				
Pre treatment	3.12	2.08	2.29	0.497
Post treatment	3.22	2.70	2.04	

SD: standard deviation.

When compared by HCV genotype, there was no significant difference in the prevalence of patients with IR either on pre or post treatment. It was observed that 52.2% of pre-treatment patients with genotype 3 had IR, with an increase to 73.9% post treatment. Regarding non-3 genotype IR, pre and post treatment prevalence were, respectively, 52.8% and 61.1%.

Patients, regardless of T2D status, tended to gain weight up to six months after SVR, but this tendency was not sustained as of the 12-month mark ($P=0.131$) (FIGURE 2).

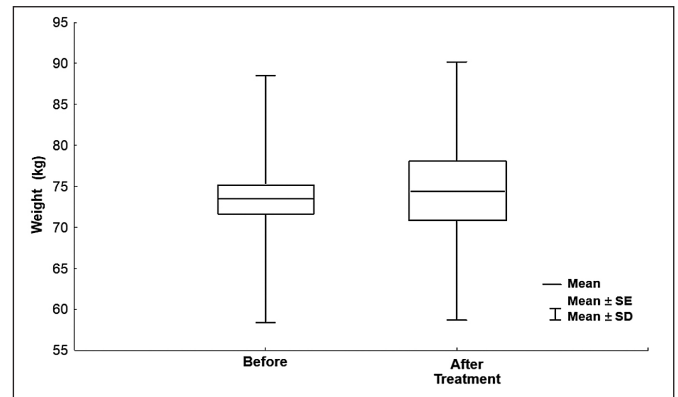


FIGURE 2. Weight variation before chronic hepatitis C treatment and 12 months after therapy.

DISCUSSION

IR and diabetes mellitus and their association with chronic hepatitis C is a recurrent theme in Hepatology literature, and said diseases are again in focus since the emergence of new DAA medications, responsible for providing a treatment with few side effects and better rates of SVR. Although well documented, the precise way the chronic hepatitis C leads to glucose intolerance isn't yet fully understood^(5,22,24,35,36,37). The systemic inflammatory response allied to a malfunctioning glucose metabolism when the hepatic disease is on an advanced level are thought to contribute to this process^(22,24,35,37,38). In this study, 28% of the patients were diabetic, a higher number than the one found in the general population⁽³¹⁾.

The exact effects of virus C treatment on glucose profile are still not completely known, although some studies show a direct relation between SVR and decreasing IR^(39,40,41,42,43). Elhelbawy et al., when researching 511 patients treated for HCC with the new DAAs, showed a significant reduction on IR⁽⁴⁴⁾. A study by Ciancio et al. on 101 patients shares this conclusion, while also demonstrating a decrease in fasting glucose and glycated haemoglobin⁽⁴⁵⁾. In the present study, even though patients had diminishing insulin and fasting glucose levels and the time range was extended to 12 months, there was no IR improvement – when calculated with HOMA-IR - after SVR with the new DAA.

Previous studies had already showed the same results. Stine et al., when studying a group of 175 patients with chronic hepatitis C treated with DAAs, couldn't show a statistical significance in glucose profile before and after treatment⁽⁴⁶⁾. Those results were also shared by Chaudhury et al., who did not identify sustained benefits to glycaemic levels following HCV clearance irrespective of HIV, diabetes or fibrosis stage⁽⁴⁷⁾. It's interesting to note that our patients had higher levels of HOMA-IR both before and after SVR when compared to other studies^(44,48), which could also justify our findings.

It must be said that weight is an important variable which directly affects IR, and it could be one of the major issues impacting the aforementioned studies, as well as the one presented here. An overall improvement in health during and after treatment with DAAs, including the return of normal appetite, could have resulted in weight gain at a first moment, leading to a worsening in IR, as observed in this study. Similarly, weight loss is one of the side effects of Interferon, one of the commonest drugs used in older regimens, and the use of this particular drug could have significantly impacted the data on previous researches.

The different outcomes in research could be explained by previous characteristics of the studied population. While in the general population of the study conducted by Andrade et al. there was an increase of glucose and HOMA-IR in the 12th week after completing treatment, the same could not be observed if diabetic patients and those with previously normal HOMA-IR were excluded⁽⁴⁹⁾.

In accordance with the current literature, there was no correlation in this study between IR and age, virus C genotype or viral load^(50,51).

This research has some limitations. Although significant, the number of patients is still small, and T2D markers may be influenced by other issues that affect cirrhotic patients – glycated haemoglobin, for example, has its accuracy decreased by anaemia and hypersplenism, and it should also be remembered that HOMA-IR doesn't have an unanimous cut-off. Moreover, much of our population consisted of patients with advanced liver fibrosis, which is notoriously associated with poorer patient outcome and could have influenced this study's results as well, reinforcing the need to treat all patients with chronic hepatitis C, and not only those with end-stage disease. This is especially true regarding insulin resistance, when precocious institution of treatment could lead to improvement not only on the problem itself, but also its pos-

sible complications. Lastly, patients from different studies are not completely homogenous, with different genetics and environmental circumstances impacting directly on results.

CONCLUSION

In this study, obtaining SVR did not result in improvement of IR according to the HOMA model collected 12 months after the end of treatment with the new direct acting antivirals. Furthermore, while patients gained weight after a year from the cure, it was not significant.

Authors' contribution

Strauhs-Nitsch L, Campiolo MF: data collection. Morsoletto DBG, Pissaia Junior A, Ivantes CAP: writing of text.

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RESUMO – Contexto – A hepatite C crônica ainda figura como importante causa de morbimortalidade na população brasileira, e está associada a alterações metabólicas, incluindo a resistência insulínica (RI), que pode ser avaliada pelo índice HOMA-IR. A RI pode inclusive implicar em menores taxas de reposta virológica sustentada (RVS) em certos regimes terapêuticos e à uma mais rápida progressão para fibrose hepática avançada. Com o advento dos novos antivirais de ação direta (DAA) oferecidos para hepatite C, há crescente necessidade de observar o impacto dos mesmos no perfil de RI em pacientes submetidos à tais terapêuticas. **Objetivo** – 1) Comparar os valores do HOMA-IR dos pacientes com hepatite C crônica antes do tratamento com os DAAs com os valores deste índice após 12 meses do término do tratamento com RVS. 2) Avaliar evolução do peso após obtenção da cura da hepatite C crônica. **Métodos** – Foram incluídos pacientes maiores de 18 anos de dois serviços terciários de Curitiba – PR, de ambos os sexos, portadores de hepatite C crônica, com tratamento com os antivirais de ação direta, no período de julho de 2015 a setembro de 2017. Tais pacientes também foram submetidos a dosagem dos níveis de insulina de jejum, glicemia de jejum e hemoglobina glicada antes de iniciar o tratamento da hepatite C e até 12 meses após o término. Também foram utilizados dados como idade, sexo, grau de fibrose hepática, índice de massa corporal, circunferência abdominal, genótipo viral e presença de diabetes mellitus antes e depois do tratamento. A RI foi estimada antes e após 12 meses do término do tratamento e calculada pelo HOMA-IR. Os resultados de variáveis quantitativas foram descritos por médias, medianas, valores mínimos, valores máximos e desvios padrões. Valores de $P < 0,05$ indicaram significância estatística. **Resultados** – Foram incluídos 75 pacientes no estudo com média de idade de 55,2 anos, sendo 60% do sexo masculino. Destes pacientes, 43 tinham fibrose avançada. Vinte e um (28%) pacientes tinham o diagnóstico de diabetes mellitus. A RI foi observada em 31 (41,3%) pacientes antes do tratamento antiviral, sendo que este número aumentou para 39 (52%) de acordo com a dosagem do HOMA-IR 12 meses após o término do tratamento. Não houve diferença estatística entre os valores de insulina, glicemia e HOMA-IR antes e após a cura da hepatite. Houve um ganho de peso inicial após a obtenção da cura da hepatite C, mas que não se manteve ao final do estudo. **Conclusão** – Não foi vista diferença estatística significativa entre os valores do HOMA-IR apresentados pelos pacientes portadores de hepatite C crônica antes do tratamento e 12 meses após a cura da doença. Embora tenha ocorrido ganho de peso após obtenção da cura da doença, este não se deu de forma estatisticamente significativa ($P = 0,131$) ao final de um ano.

DESCRITORES – Hepatite C. Resistência à insulina. Diabetes mellitus. Antivirais.

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