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Can the degree of hepatic fibrosis and hepatitis C virus characteristics influence glucose and lipid metabolism in sustained virological response with direct acting antivirals?

Fibrose hepática e características do vírus da hepatite C podem influenciar alterações no metabolismo glicídico e lipídico na resposta virológica sustentada com Antivirais de Ação Direta?

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Abstract:

Aims: To assess the metabolic impact the sustained virological response (SVR) using direct acting antivirals according to liver fibrosis degree and virus characteristics in patients with chronic hepatitis C (HCV). **Methods:** Prospective pre-post intervention study. Patients were categorized according to genotypes (G) and fibrosis (F) categories. Glucose metabolism was evaluated using: HOMA-IR, HOMA-β, TyG, and HbA1c and lipid metabolism: total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins and triglycerides. Statistical analysis involved paired t-test to compare the means of the variables between the pretreatment and SVR periods. A p-value of <0.05 was considered as significant. **Results:** Among 273 patients, average age of 57 years; 45.8% prediabetic; 18.3% diabetic; 28.6% cirrhotic, and 33.7% had mild or absent fibrosis (F0/F1); with respect to genotypes, 53.9% G1: subtypes G1a (46.60%) and G1b (53.40%). The lipid profile showed a significant increase in triglycerides, TC, and LDL in the SVR. The HOMA-IR index showed no significant differences, while the HOMA-β index significantly increased in patients with advanced fibrosis (F3/F4) (p=0.044). The TyG index significantly increased in patients F0/F1 fibrosis (p=0.002), patients without cirrhosis (p=0.005), patients G1 without cirrhosis (p=0.024), and patients G1a without cirrhosis (p=0.021). HbA1c decreased in patients F3/F4 fibrosis (p=0.038), patients without cirrhosis (p=0.010), patients G1a without cirrhosis (p=0.015), and patients non-1 genotype without cirrhosis (p=0.010). **Final considerations:** The SVR showed variable metabolic influences, indicating potential lipid profile impairment and glycemic profile improvement. Differences were observed depending on the degree of fibrosis and genotypes, underscoring the importance of recognizing the peculiarities of the constituted samples.

Keywords: Direct-acting antivirals; Insulin resistance; Hepatitis C; Hepatic fibrosis; Glucose and lipid metabolism

Resumo:

Objetivo: Avaliar o impacto metabólico da resposta virológica sustentada com antivirais de ação direta de acordo com o grau de fibrose hepática e características virais em pacientes com hepatite crônica C. **Métodos:** Estudo prospectivo, pré e pós-intervenção. Os pacientes foram categorizados conforme os genótipos e o grau de fibrose. O metabolismo glicídico foi avaliado usando: índice HOMA-IR; HOMA-β, TyG e HbA1c; e o metabolismo lipídico: colesterol total (CT), lipoproteína de baixa densidade (LDL), lipoproteína de alta densidade (HDL) e triglicerídeos. Na análise estatística utilizou-se teste t pareado para comparar a média das variáveis entre o pré-tratamento e a RVS.

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Adotado p < 0,05 como significante. **Resultados:** Amostra de 273 pacientes, média da idade 57 anos; 45,8% pré-diabéticos; 18,3% diabéticos; 28,6% cirróticos; 33,7% tinham fibrose leve ou ausente (F0/F1) e quanto aos genótipos, 53,9% G1: G1, subtipo a, 46,60% e G1b 53.40%. No perfil lipídico observou-se aumento significativo nos triglicerídeos, CT e no LDL na SVR. No índice HOMA-IR não houve diferenças significativa, enquanto no índice HOMA-β observou-se aumento significativo nos pacientes com fibrose avançada (F3/F4) (*p*=0,044). No índice TyG aumento significativo no grupo de pacientes com fibrose leve ou ausente (*p*=0,002), no grupo geral sem cirrose (*p*=0.005), naqueles sem cirrose e com genótipo1 (*p*=0.024) e nos pacientes sem cirrose genótipo1 subtipo a (*p*=0.021). Já a HbA1c diminuiu nos pacientes F3/F4 (*p*=0.038), pacientes sem cirrose (p=0.010), pacientes G1a sem cirrose (*p*=0.015) e naqueles não genótipo 1 sem cirrose (*p*=0.010). **Considerações finais**: A RVS demonstrou influências metabólicas variáveis. Indicando potencial piora no perfil lipídico e melhora no perfil glicídico. Diferenças foram observadas dependendo do grau de fibrose e do genótipo. ressaltando a importância de reconhecer as peculiaridades das amostras constituídas.

Palavras-chave: Antivirais de ação direta; Resistência à insulina; Hepatite C; Fibrose hepática; Metabolismo glicídico e lipídico

1 INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) in patients with chronic hepatitis C (HCV) may surpass that of the general population[1,2]. Chronic HCV infection, through its progressive worsening of liver disease, heightens the risk of T2DM[1].

While the effects of chronic HCV infection and the advantages of sustained virological response (SVR) on liver diseases have been extensively researched, the systemic consequences of persistent viral infection, particularly the extrahepatic sequelae, remain less well known[2]. However, it is projected that approximately two-thirds of patients may experience extrahepatic manifestations[3], with significant metabolic alterations[2].

Insulin metabolism can be adversely affected by advanced liver fibrosis[4]. Nevertheless, Hepatitis C Virus (HCV) could induce insulin resistance (IR) irrespective of liver disease severity, indicating that this virus can trigger this metabolic effect even during the initial stages of the disease[4]. Moreover, a rapid progression of hepatic fibrosis, steatosis, and hepatocellular carcinoma has been linked with IR[4].

HCV notably impacts lipid metabolic pathways, as evidenced by significant alterations following SVR, suggesting a direct viral effect[5]. Furthermore, HCV's role in modulating the metabolic pathways of intrahepatic cholesterol biosynthesis to facilitate viral replication is also significant, with substantial changes in lipid metabolism observed in SVR[5].

Several clinical studies have indicated enhancements in glucose metabolism following antiviral treatment[6,7]. Conversely, other research has identified significant elevations in total cholesterol (TC), low-density lipoproteins (LDL), and triglycerides, but not high-density lipoproteins (HDL), associated with SVR[8,9]. Other authors[10,11] have reported an increase in cholesterol, LDL, and triglyceride levels post-SVR. Therefore, elucidating

the impact of HCV eradication on glucose and lipid homeostasis could strengthen the understanding of these intriguing concepts and uncertainties.

The homeostasis model assessment (HOMA) indices are frequently utilized to evaluate the impact of SVR on glucose metabolism. The HOMA index, a validated tool, is used to estimate IR (HOMA-IR) and large-scale β, cell function (HOMA-β,)[12]. The triglyceride-glucose (TyG) index, another measure of IR, is calculated as the product of fasting triglyceride and glycemia levels[13]. In routine clinical practice, glycated hemoglobin (HbA1c) is the most commonly employed test for assessing glucose metabolism[14]. HCV can induce hypolipidemia, and its life cycle is dependent on the host cells cholesterol metabolism, which may be evident in laboratory tests[15].

Treatment using direct-acting antivirals (DAAs) yields an SVR rate exceeding 95%[16]. Given the effectiveness of current therapies and the correlation between HCV and systemic disorders, it is anticipated that virus eradication will enhance metabolic parameters and decrease the rates of T2DM and IR in patients with chronic infection[5]. Nevertheless, the impact of SVR on glycemic control remains a contentious issue[17,18]. Factors such as the degree of fibrosis and viral genotypic characteristics[2] are significant variables that may lead to inconsistencies in the results.

Although findings vary, numerous studies have highlighted a correlation between chronic HCV infection and IR, emphasizing the potential advantages for glucose metabolism in SVR[2,19]. However, both beneficial and detrimental metabolic alterations have been reported in association with DAA treatment[7,20]. Therefore, it is imperative to investigate this intricate topic across diverse populations.

The objective of this study was to analyze and compare glucose and lipid metabolism in patients with chronic hepatitis C. These patients were treated with DAAs, and the study examined their pretreatment and SVR in relation to hepatic fibrosis and viral characteristics.

2 METHODS

This pre-post intervention study assessed all patients with chronic hepatitis C who were eligible for treatment with DAAs at the Dr. Miguel Riet Corrêa Jr. University Hospital of the Federal University of Rio Grande (FURG) between March 2018 and December 2019. The treatment adhered to the inclusion and duration criteria outlined in the Clinical Protocol and Therapeutic Guidelines for Hepatitis C and Coinfections 2018/2019.

The inclusion criteria encompassed individuals aged ≥18 years, diagnosed with chronic liver disease C, compensated cirrhosis (Child-Pugh stage A), and residing in either Rio Grande or São José do Norte municipalities. The exclusion criteria included the presence of decompensated cirrhosis (Child-Pugh stages B and C), co-infection with

chronic hepatitis B virus or human immunodeficiency virus, alcoholic liver disease, severe psychiatric disorders, chronic pancreatitis, chronic kidney failure, transplant recipients, type 1 DM, steroid or anabolic usage, alcohol consumption exceeding 50 g/day, and failure to achieve SVR.

During the study period, 480 patients received treatment. However, 151 of these patients were excluded, and 38 refused to participate. Consequently, 291 patients were initially selected for the study. Out of these, 13 (4.5%) did not achieve SVR, and five (1.7%) failed to complete the tests or return for consultations, resulting in their loss to follow-up. Ultimately, 273 patients were included in the final analysis. These patients were then subjected to a precoded standard questionnaire designed to evaluate sociodemographic and clinical aspects related to Hepatitis C and T2DM. Upon completion of the questionnaire, anthropometric measurements, including weight, height, waist circumference (WC), and abdominal circumference, were taken.

WC was measured at the midpoint between the last rib and the iliac crest, following normal expiration. For men, a WC measurement of ≤93 cm and for women, ≤ 79 cm, was deemed adequate. The categorization of Body mass index (BMI) adhered to the 2016 Brazilian Guidelines for Obesity.

The criteria outlined in the 2019-2020 Guidelines of the Brazilian Society of Diabetes were used to diagnose T2DM, prediabetes, and normoglycemia. Patients who were classified as having diabetes received their diagnosis prior to the initiation of HCV treatment.

Fibrosis (F) was assessed using hepatic elastography (KPa ≤ 7.0 = F1, KPa ≥ 7.5-10 = F2, KPa ≥ 10-14 = F3, KPa ≥ 14 = F4), clinical indicators of liver cirrhosis, and the presence of esophageal or gastric fundus varicose veins as determined by upper digestive endoscopy examination. Additionally, imaging findings suggestive of portal hypertension or chronic hepatopathy were considered[16]. The METAVIR scale was employed for histopathological classification. In our analyses, we categorized F0/F1 as absent or mild fibrosis; F2, moderate fibrosis; and F3/F4, advanced fibrosis or cirrhose. When referring to patients with cirrhosis, we specifically considered the F4 group. The non-cirrhotic subgroup included patients classified as F0/F1/F2/F3. For analyses involving patients with cirrhosis, the F4 patient group was again considered separately. We also created subgroups based on genotypes and genotype 1 subtypes, each associated with different degrees of fibrosis.

Characteristics of the virus, including genotypes (G), G1 subtypes a and b, were assessed using real-time polymerase chain reaction (PCR). Quantitative HCV research was also conducted. An undetectable viral load following the 12th week of treatment was deemed indicative of SVR[16].

The evaluation of glucose metabolism utilized the following indices: HOMA-IR[12], HOMA-β[12], TyG[13], and HbA1c[14]. These parameters were assessed at the initiation of treatment and upon achieving SVR.

The evaluation of lipid metabolism utilized TC, LDL, HDL, and triglycerides.

Patients were categorized into various groups and subgroups based on the severity of fibrosis. This classification was done to discern the distinct impacts of each degree of fibrosis on glucose and lipid metabolism.

The data for this analysis were exported to the SPSS 20 program, where the sample was initially categorized and described. Subsequently, a comparison of the means of the variables was conducted in the pretreatment and SVR stages using the paired analysis method via the T test. Variables with a *p*-value less than 0.05 were deemed significant. The project received approval from the FURG health area's ethics and research committee (CEPAS), under process number 23116.00516/2018-56.

3 RESULTS

Out of the 273 participants in the study, 263 (96.3%) had not received any prior treatment ("naive"), while 10 (3.7%) had previously been treated ("experienced") with PEG-interferon and ribavirin. The average age of the participants was 57 years, with 70.7% identifying as white and 52.7% as male. In terms of anthropometric data, 200 (70.7%) had an abdominal WC exceeding the acceptable values for their respective sexes, and the average BMI was 27.59. With respect to genotypes, 148 (53.9%) were G1: subtypes G1a (46.60%) and G1b (53.40%); 38 (14%), G2; and 87 (32.1%), G3. In terms of liver damage, 78 (28.6%) were cirrhotic, and 92 (33.7%) were classified as having mild or no fibrosis (F0/F1). Most patients (125) were prediabetic (45.8%), and 50 were diabetic (18.3%). In terms of lipid profiles, we observed a significant increase in triglycerides (from 95.44 to 104.47; p= 0.006), TC (from 166.37 to 185.52; $p < 0.001$), and LDL (from 97.30 to 111.80; $p<0.001$) in SVR but not in HDL (from 49.59 to 50.26; p= 0.652) (Table 1).

Table 1 – Anthropometric and laboratory data and comparison parameters

	N (%)	Pretreatment	SVR	*p*- value
Age (Mean ±SD)				
≤ 54 years old	98 (35.9)	57.03(±11.11)		
55 to 64 years old	113 (41.4)			
≥ 65 years old	62 (22.7)			
Color				
White	193 (70.7)			
Nonwhite	80 (29.3)			

Table 1 – Anthropometric and laboratory data and comparison parameters

(Continued)

	N (%)	Pretreatment	SVR	*p*- value
Genre				
Male	144 (52.7)			
Female	129 (47.3)			
Color				
White	193 (70.7)			
Nonwhite	80 (29.3)			
Weight (Mean ±SD)		73.21 (±14.72)	73.54 (±14.69)	0.127
WC Abdominal (Mean ±SD)		94.38 (±11.87)	94.04 (±11.99)	0.206
Adequate	73 (29.3)			
Inadequate	200 (70.7)			
BMI (Mean ±SD)		27.59 (±4,76)	27.73 (±4.84)	0.093
Glucose Profile (Mean ±SD)		107.84 (±27.29)	107.79 (±31.70)	0.976
Normal Blood Glucose	98 (35.9)			
Prediabetes	125 (45.8)			
Diabetes	50 (18.3)			
Cirrhosis				
Yes	78 (28.57)			
No	195 (71.43)			
Degrees of Fibrosis				
F0-F1	92 (33.7)			
F2	65 (23.8)			
F3	38 (13.9)			
F4	78 (28.6)			
Profile triglycerides (Mean ±SD)				
Genotype 1 (148)		101.87(±66.30)	105.30(±66.47)	0.416
Genotype 2 (38)		104.95(±49.45)	109.51(±54.57)	0.563
Genotype 3 (87)		79.85(±31.56)	100.94(±76.15)	0.031

Table 1 – Anthropometric and laboratory data and comparison parameters

(Conclusion)

	N (%)	Pretreatment	SVR	*p*- value
Laboratories (Mean ±SD)				
Platelets		195.560(±517)	200.140(±58.292)	0,039
Albumin		4.04 (±0.44)	4.35 (±0.32)	<0.001
AST		63.67 (±51.87)	22.42 (±8.18)	<0.001
ALT		87.30 (±71.29)	20.59 (±12.14)	<0.001
Gamma GT		78.39 (±92.93)	30.45 (±31.43)	<0.001
AF		120.43 (±76.37)	167.51 (±87.49)	<0.001
BT		0.72 (± 0.36)	0.66 (±0.36)	0.003
INR		1.05 (±0.11)	1.04 (±0.13)	0.290
Total Cholesterol		166.37 (±36.91)	185.52 (±38.41)	<0.001
LDL		97.30 (±33.86)	111.80 (±36.66)	<0.001
HDL		49.59 (±14.23)	50.26 (±13.66)	0.652
Triglycerides		95.44 (±55.67)	104.47 (±67.50)	0.006

AF: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BT: total bilirubin; w/: with; FG: fasting glucose; GT: glutamyl transferase; HDL: high density lipoprotein; LDL: low density lipoprotein; N: number; SD: standard deviation; SVR: sustained viral response; WC: waist circumference.

Upon analyzing potential alterations in metabolic parameters according to varying degrees of fibrosis, no significant differences were observed between pretreatment and SVR using the HOMA-IR index. However, a significant increase was identified in patients with advanced fibrosis (F3/F4) when using HOMA-β (93.49 to 108.12; *p*=0.044) (Table 2).

We observed a significant increase in the TyG index among F0/F1 patients (from 4.51 to 4.58; *p*=0.002), patients with cirrhosis (from 4.54 to 4.58; *p*=0.005), patients with G1 without cirrhosis (from 4.54 to 4.59; *p*=0.024), and patients with G1a without cirrhosis (from 4.55 to 4.63; *p*=0.021). Conversely, a significant decrease in the TyG index was observed among patients with cirrhosis with G1 (from 4.61 to 4.52; *p*=0.007) and those with G1b (from 4.61 to 4.52; *p*=0.021). Upon analyzing the HbA1c values in the pretreatment and SVR groups, we noted a significant decrease among F3/F4 patients (from 5.90 to 5.72; *p*=0.038), patients without cirrhosis (from 5.67 to 5.53; *p*=0.010), patients with G1a without cirrhosis (from 5.70 to 5.47; *p*=0.015), and patients with non-1 genotype (GN1) without cirrhosis (from 5.73 to 5.53; *p*=0.010) (Table 3).

Table 2 – Analysis of the HOMA-IR index and of the HOMA-β index in relation to the degree of liver fibrosis

	HOMA-IR pretreatment Mean (SD)	**HOMA-IR pretreatment CI 95%**	**HOMA-IR SVR Mean (SD)**	**HOMA-IR SVR CI 95%**	***p-value***
Fibrosis degree					
Mild (F0-F1) (92)	2.10 (±1.33)	1.86 – 2.36	2.36 (±1.43)	2.10 – 2.65	0.072
Moderate (F2) (65)	2.35 (±1.73)	1.93 – 2.81	2.38 (±1.66)	2.00 – 2.79	0.878
Advanced (F3-F4) (116)	2.93 (±2.46)	2.52 – 3.43	3.23 (±3.36)	2.70 – 3.94	0.165
Cirrhosis					
Yes (78)	3.27 (±2.76)	2.70 – 3.96	3.74 (±3.90)	3.03 – 4.78	0.100
No (195)	2.21 (±1.50)	2.01 – 2.43	2.33 (±1.48)	2.12 – 2.43	0.205
Cirrhosis/genotype (78)					
G1 (41)	3.09 (±2.19)	2.44 – 3.76	3.34 (±2.46)	2.60 – 4.11	0.394
G1 a (17)	2.92 (±1.86)	2.10 – 3.86	3.04 (±1.93)	2.22 – 4.04	0.719
G1 b (23)	3.13(±2+45)	2.24 – 4.21	3.52 (±2.85)	2.52 – 4.82	0.402
GN1(37)	3.47 (±3.32)	2.50 - 4.72	4.21 (±5.07)	2.89 – 6.32	0.172
Nocirrhosis/ G (195)					
G1 (102)	2.17 (±1.51)	1.89 – 2.48	2.39 (±1.52)	2.11 – 2.70	0.138
G1 a (50)	2.36 (±1.66)	1.94 – 2.85	2.79 (±1.73)	2.31 – 3.29	0.082
G1 b (52)	1.96 (± 1.34)	1.66 – 2.39	2.00 (±1.19)	1.71 – 2.33	0.905
GN1 (93)	2.30 (±1.52)	1.99 – 2.63	2.30 (±1.46)	2.00 – 2.63	1.000
	HOMA-β pretreatment Mean (SD)	**HOMA-β pretreatment CI 95%**	**HOMA-β SVR Mean (SD)**	**HOMA-β SVR CI 95%**	
Fibrosis degree			93.31 (±54.97)		
Mild (F0-F1) (92)	88.48 (± 65.09)	75.21-101.79	87.72 (±64.10)	82.41 -104.56	0.477
Moderate (F2) (65)	74.89 (±51.68)	63.03-87.43	108.12 (±81.49)	72.32-104.53	0.056
Advanced (F3- F4) (116)	93.49 (±58.89)	82.55-104.72		94.39-124.83	0.044
Cirrhosis			116.27 (±		
Yes (78)	97.00 (± 60.50)	83.78-111.03	89.00)	98.67- 138.0	0.061
No (195)	83.49 (±59.12)	75.10 - 91.71	91.03 (±59.00)	83.12-99.53	0.079
Cirrhosis/ genotype (78)					
G1 (41)	100 (± 63.30)	81.59 -118.61	128.09 ±106.51)	100.57 165.27	0.084
G1 a (17)	81.56 (± 48.54)	59.50–105.04	139.65	82.89-223.13	0.086
G1 b (23)	108.74 (±68.23)	82.78-137.32	(±149.33)	92.91-142.56	0.592
GN1 (37)	93.58 (±57.84)	75.66-113.30	116.76 (±63.13)	83.20-123.85	0.425
No Cirrhosis/ G (195)			102.80 (±62.33)		
G1 (102)	85.66 (±62.93)	74.48 – 98.26		83.75– 107.51	0.117
G1 a (50)	94.95 (±73.20)	77.39 -117.84	95.29 (±65.59)	92.37 -133.08	0.121
G1 b (52)	76.72 (±50.29)	64.09 - 91.55	110.74 (±73.65)	66.59 – 96.26	0.603
GN1 (93)	82.59 (±55.84)	71.36 – 95.74	80.45 (±53.39)	75.54 – 97.99	0.471
			86.73 (±51.63)		

HOMA-IR: Homeostasis Model Assessment-insulin resistance; HOMA-β: Homeostasis Model Assessment-β cell; SD: standard deviation; SVR: Sustained Viral Response; CI: confidence interval; F: fibrosis; G: genotype.; G1 a: genotype subtype a; G1b: genotype 1 subtype b; GN1: non-1 genotypes

Table 3 – Analysis of TyG and HbA1c in relation to the degree of liver fibrosis

	TyG pretreatment Mean (SD)	TyG pretreatment CI 95%	TyG pretreatment CI 95%	TyG SVR CI 95%	*p-value*
Degrees of Fibrosis					
Mild (F0-F1) (92)	4.51 (±0.26)	4.46 – 4.57	4.58 (±0.29)	4.53 – 4.65	0.002
Moderate (F2) (63)	4.57(±0.25)	4.51 – 4.64	4.60 (±0.31)	4.53 – 4.69	0.379
Advanced (F3-F4) (110)	4.56 (±0.27)	4.51 – 4.61	4.55 (±0,29)	4.50 – 4.61	0.673
Cirrhosis					
Yes (74)	5.71 (±0.91)	5.57 - 5.87	4.57 (±0.31)	4.49 – 4.64	0.936
No (190)	4.54 (±0.26)	4.50 – 4.58	4.58 (±0.29)	4.54 – 4.62	0.005
Cirrhosis/ G (74)					
G1 (41)	4.61 (±0.21)	4.54 – 4.68	4.52 (±0.18)	4.46 – 4.58	0.007
G1 a (17)	4.61 (±0.22)	4.51 – 4.72	4.51 (±0.16)	4.44 – 4.58	0.078
G1 b (23)	4.61 (±0.22)	4.52 – 4.70	4.52 (±0.19)	4.44 – 4.60	0.021
GN1 (33)	4.52 (±0.33)	4.41 – 4.64	4.62 (±0.41)	4.48 – 4.76	0.068
No Cirrhosis/ G (190)					
G1 (102)	4.54 (±0.27)	4.49 – 4.60	4.59 (±0.29)	4.54 – 4.65	0.024
G1 a (50)	4.55 (±0.25)	4.48 – 4.63	4.63 (±0.27)	4.55 – 4.71	0.021
G1 b (52)	4.54 (±0.30)	4.46 – 4.62	4.56 (±0.30)	4.67 – 4.91	0.411
GN1 (88)	4.52 (±0,24)	4.47 – 4.57	4.55 (±0.29)	4.49 – 4.62	0.115
	HbA1c pretreatment Mean (SD)	**HbA1c pretreatment CI 95%**	**HbA1c SVR Mean (SD)**	**HbA1c SVR CI 95%**	
Degrees of Fibrosis					
Mild (F0-F1) (92)	5.60 (±0.72)	5.46 – 5.75	5.47 (±0.75)	5.33 – 5.64	0.059
Moderate (F2) (65)	5.62 (±0.83)	5.44 – 5.83	5.54 (±0.82)	5.36 – 5.73	0.416
Advanced (F3-F4) (116)	5.90 (±1.18)	5.70 – 6.13	5.72 (±1.10)	5.54 – 5.93	0.038
Cirrhosis					
Yes (78)	5.89 (±1.20)	5.64 – 6.19	5.74 (±1.23)	5.49 – 6.06	0.144
No (195)	5.67 (±0.86)	5.56 – 5.80	5.53 (±0.78)	5.43 – 5.65	0.010
Cirrhosis/ G (78)					
G1 (41)	5.77 (±1.24)	5.44 – 6.16	5.57 (±0.86)	5.34 - 5.85	0.137
G1 a (17)	5.97 (±1.54)	5.39 – 6.85	5.58 (±1.12)	5.13 - 6.20	0.109
G1 b (23)	5.60 (±0.87)	5.31 – 6.60	5.48 (±0.56)	5.27 – 5.75	0.481
GN1 (37)	6.03 (±1.16)	5.69 – 6.39	5.94 (±1.54)	5.52 – 6.45	0.586
No cirrhosis/ G (195)					
G1 (102)	5.58 (±0.76)	5.45 - 5.73	5.52 (±0.75)	5.38 – 5.67	0.383
G1 a (50)	5.70 (±0.86)	5.50 – 5.98	5.47 (±0.54)	5.33 – 5.62	0.015
G1 b (52)	5.47 (±0.64)	5.37 – 5.65	5.57(±0.91)	5.36 – 5.86	0.310
GN1 (93)	5.73 (±0.81)	5.55 – 5.90	5.53 (±0.82)	5.36 – 5.71	0.010

TyG: triglycerides and glucose; HbA1c: glycated hemoglobin; SD: standard deviation; SVR: Sustained Viral Response; CI: confidence interval; F: fibrosis; G: genotype.; G1 a: genotype 1 subtype a; G1b: genotype 1 subtype b; GN1: non-1 genotypes

4 DISCUSSION

Herein, we found that 64.1% of patients exhibited glucose metabolism disorders. This is significantly higher than the general Brazilian population, where 7.5% to 18.5% are prediabetic[21] and 7.7% are diabetic[22]. These findings align with the hypothesis that there is an association between HCV, IR, and T2DM, corroborating the results of other studies[15,23]. We noted that most patients were either overweight or obese and had an excessive abdominal WC. These factors could have initially influenced the values obtained. However, these parameters remained consistent throughout the study, and no evolutionary changes were observed that could have affected the comparison of the metabolic effects of treatment with DAAs.

The impact of antiviral treatment on lipid metabolism remains unclear[8]. In our study, regarding laboratory tests, we noted a significant rise in TC, LDL, and triglycerides but not in HDL. Studies involving patients with genotype 1 typically reported a significant increase in TC, LDL, and triglycerides levels after SVR[7,24], which is in line with our findings. Carvalho *et al.*[25] highlighted an elevated risk of cardiovascular events following treatment with DAAs, underscoring the significance of the lipid changes we observed.

Upon analyzing the metabolic impact of SVR in relation to varying degrees of fibrosis, we detected no significant alterations in the IR as evaluated by HOMA-IR. However, we observed an improvement in β cell function, as indicated by HOMA-β, in the F3/F4 patient group. Similarly, HbA1c demonstrated a significant improvement in patients without cirrhosis and those with advanced fibrosis. These results demonstrate the complex associations of fibrosis and glucose metabolism. Conversely, the TyG index deteriorated in F0/F1 and patients without cirrhosis. These results imply that the reversal of the hypolipidemic effect triggered by HCV is more pronounced in patients less affected by fibrosis.

In our subgroup analysis correlating varying degrees of fibrosis with genotypes, we found no significant differences in HOMA-IR and HOMA-β. This contrasts with a prospective study[26] involving 138 patients, of which 68.8% were cirrhotic and 68% had IR. Using the HOMA-IR index, this study reported a significant decrease in baseline for SVR (3.0 vs. 1.8; $p < 0.0010$). However, it is important to note that patients with diabetes were excluded from that study, creating a significant metabolic difference compared to our patient group. Our findings did not align with those of Boraie *et al.*[27] but were consistent with the results of Doyle *et al.*[24], where the HOMA-IR index remained unchanged in F0/F1, patients without cirrhosis, and patients with G1 and G1a without cirrhosis.

Significant improvement in the TyG index was observed in patients with G1 and G1b cirrhosis. Conversely, a deterioration of the TyG index was noted in the F0/F1 patient

subgroups and in patients with G1 and G1a without cirrhosis. This pattern suggests that G1, and particularly G1a, exert a hypolipidemic effect that is more pronounced in patients without cirrhosis. The eradication of these genotypes leads to an increase in triglycerides and, consequently, the TyG index. Cheng et al study[10] reported a significant increase in triglycerides only in patients without advanced fibrosis. Gitto et al research[28], which comprised a large proportion of patients with cirrhosis (81%), found no changes in triglyceride levels in more severe cases. Our results align with these findings, indicating a higher likelihood of deterioration in patients without cirrhosis when evaluated using the TyG index.

Upon analyzing HbA1c, a decrease was observed in F0/F1 patients (5.60 to 5.47), with a near-significant tendency (p=0.059), and in patients with G1a without cirrhosis (5.70 to 5.47: $p < 0.015$). These findings suggest a higher likelihood of positive outcomes in patients without cirrhosis. When we included patients without cirrhosis and those with F3/F4 in the analysis, an improvement in glucose control was noted, a phenomenon not observed in patients with cirrhosis alone. A retrospective study by Weidner *et al.*[29] involving 281 patients underscored the beneficial impact of SVR on glucose metabolism but also revealed that this effect did not extend to patients with cirrhosis. We noted an improvement in HbA1c in patients without cirrhosis and even in those with F3/F4, indicating advanced hepatic fibrosis. This observation aligns with a cohort study[18] involving 205 patients, where early improvement in glycemic control following viral clearance was noted, even in patients with severe hepatic fibrosis. Other researchers[6,7,27] also reported that HCV eradication by DAAs led to a concurrent decrease in IR and an improvement in glycemic control in patients with T2DM, even those with severe hepatic fibrosis. In a study[30] involving 175 patients, 80.8% with G1 and 61.5% with cirrhosis, no improvement in HbA1c was found in SVR, a finding that aligns with our results, as we observed no significant improvement in HbA1c when we included patients with G1 and cirrhosis in the analysis.

Our study had certain limitations. A significant proportion of our sample comprised overweight and obese patients, potentially obscuring a more generalized beneficial effect of SVR. Additionally, we cannot rule out the potential impact of diet-related variations on the analysis of fasting triglyceride levels, which could compromise the reliability of the TyG index. This would subsequently complicate the interpretation of the effects of reduced lipolysis suppression following HCV cure. Furthermore, the relatively brief follow-up period for these patients constitutes another limitation.

Our study consistently found that the HOMA-IR index failed to detect significant changes in IR post-SVR across various groups and subgroups. Notably, TyG improved in patients with G1 and G1b and with cirrhosis. HbA1c showed improvement in the following

subgroups: F3/F4; patients without cirrhosis; patients without cirrhosis/G1b; and patients without cirrhosis/GN1. These results suggest that achieving SVR can lead to variable metabolic effects, potentially causing a deterioration in lipid profile and enhancements in the glucose profile of these individuals. We observed significant differences in the impact on glucose metabolism post-SVR, contingent on the degree of fibrosis and genotypes. Comprehending the influence of these variables underscores the significance of our study.

5 FINAL CONSIDERATIONS

This conclusion enhances our understanding of the variability in results found in existing literature. It underscores the importance of acknowledging the unique characteristics of the cases studied and the patients treated.

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CONFLICTS OF INTEREST AND FINANCING

There are no conflicts of interest, and the study was conducted without any financial assistance.

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