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Evaluation of carbohydrate and lipid metabolism dynamics in chronic HCV diabetic patients treated with direct antiviral agents

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ABSTRACT

Although Hepatitis C virus (HCV) infection has become a curable disease, the aftermath of the infection remains an important aspect to be evaluated. HCV infection is well known for its extrahepatic manifestations, mostly the tight relationship between HCV, type 2 diabetes mellitus (T2DM) and dyslipidemia. Not only HCV increases the risk of T2DM, but it also affects its control in diabetic patients, increasing the risk of diabetes related complications. Furthermore, HCV hijacks the lipid metabolism resulting in abnormalities in circulating lipids which can lead to multiple complications, such as increased atherosclerotic risk and hepatic steatosis.

Objectives. The aim of this study was to evaluate the dynamics of the parameters of carbohydrate and lipid metabolism in HCV-infected diabetic patients compared to non-diabetic patients after viral eradication.

Material and methods. This is a prospective study conducted on 100 patients with chronic HVC infection who obtained viral clearance after interferon-free treatment. 58 patients had type 2 diabetes mellitus and 42 were non-diabetic. We evaluated serum total cholesterol, triglycerides, blood glucose and glycosylated hemoglobin in both groups at treatment initiation and 1 year after. Continuous variables were expressed as mean values ± standard deviation or median, categorical variables were represented as relative or absolute frequencies. Characteristics were compared using the Mann-Whitney method or the two-sample Student's T-test method for continuous variables, Chi-square and Fischer's test for categorical variables. A p value < 0.05 was considered statistically significant.

Outcomes. The study analyzed and compared lipid and glycemic profiles of diabetic and non-diabetic HVC patients before and after viral cure.

Conclusions. 1 year after treatment initiation the changes in lipid metabolism seem to persist, carbohydrate metabolism seems to remain unchanged, with no differences between diabetic and non-diabetic patients.

Keywords: Hepatitis C virus, sustained virological response, carbohydrate metabolism, lipid metabolism, diabetes mellitus

INTRODUCTION

HCV chronic (HCV) infection is still a worldwide problem. More than 71 million people are chronically infected with HCV (over 1% of the world's population), of which 580,000 deaths are due to the long-term complications of the disease - liver cirrhosis and hepatocellular carcinoma [1]. The advent of direct acting antiviral (DAA) treatment, with an excellent efficiency of more than 95% in curing the in-

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fection and good tolerance led to the start of World Health Organization (WHO) program to eradicate HCV infection by 2030 [2]. However, currently available epidemiological data show that only 20% of HCV carriers have been diagnosed, of which only 7% have initiated antiviral treatment, with significant differences in numbers between countries [3]. To date only 12 countries meet the criteria to eradicate HCV infection. Underdiagnoses, low surveillance and high costs of diagnosis and treatment remain the main limitations to eradication [4].

Although HCV is a hepatotropic virus, studies conducted in recent decades have demonstrated the relationship between HCV and the occurrence of extrahepatic complications. However, the pathophysiological mechanisms underlying these manifestations are not fully elucidated. Most metabolic complications are thought to originate from disruption of carbohydrate and lipid metabolism [5-9].

To date there is ample evidence that HCV plays a direct role in the development of insulin resistance and type 2 diabetes mellitus (T2DM). Epidemiological studies carried out over time have shown that the prevalence of T2DM in patients infected with HCV is much higher than in the general population, varying between 13-67% depending on the stage of liver fibrosis and the time of infection [10-13]. However, not all studies have confirmed the direct link between HCV infection and the onset of T2DM, but rather the appearance of an increased risk of altered carbohydrate metabolism, thus suggesting the involvement of other variables including age, stage of liver damage and body mass index (BMI) [13]. It is also known the close connection between HCV and the lipid metabolism of the host, which the virus uses in its life cycle [14-17]. HCV circulates in the form of a lipoviral particle, associating in its composition lipids of the host. Also, in order to be internalized at the level of the hepatocyte, the virus uses cellular receptors of a lipoprotein nature [18,19] and at the intracellular level, HCV interferes and alters mainly three mechanisms of the lipid metabolism: 1. Increases lipid synthesis; 2. Inhibits mitochondrial beta oxidation, with a decrease in lipid degradation and 3. Reduction in the export of apolipoproteins, especially VLDL (very low density lipoproteins), with significant intracellular accumulation and successive decrease in the serum concentration of cholesterol and lipoproteins [20].

Subjects with insulin resistance e.g. T2DM, show increased de novo lipogenesis and increased production and decreased clearance of triglycerides, with both intracellular accumulation and increased circulating triglycerides. Thus, as insulin resistance accelerates, the prolipogenetic effects of insulin are maintained in parallel with the impairment of hepatic gluconeogenesis control, resulting in hyperglycemia and hypertriglyceridemia [21-29].

Recently, with the introduction of direct acting antivirals (DAAs) treatment, attention has turned to metabolic changes that occur after viral infection has been cured. Regarding carbohydrate metabolism, most studies have shown a net improvement in glycemic parameters. Observational studies have shown improvement in insulin resistance and a decrease in the incidence of T2DM after sustained virological response (SVR)- defined as undetectable HCV-RNA 3 months after end of treatment (EOT), a decrease in glycosylated hemoglobin after SVR and a decrease in fasting blood glucose values [28,5,30-32]. Regarding the particularities of lipid metabolism in patients cured of HCV, both in the era before DAAs and afterwards, an unfavorable evolution of the lipid profile was observed, consisting of an increase in the concentration of circulating lipids, specifically an increase in the serum concentration of cholesterol through LDL (low density lipoproteins) and VLDL fractions, but also triglycerides, with the potential to increase cardiovascular atherogenic risk [22-31].

The purpose of the present study is the dynamic evaluation of the parameters of carbohydrate and lipid metabolism in diabetic and non-diabetic HCV-infected patients who were treated with DAAs.

MATERIALS AND METHOD

This is a prospective-observational study based on a cohort of 100 patients with chronic HCV infection who were treated with DAAs at the National Institute for Infectious Diseases (INBI) "Prof. Dr. Matei Bals" during September 2018 - August 2019. The study was approved by the local Ethical Committee (register no. 7440/ 19.09.2018). Data were retrieved by revision of medical charts, laboratory data, medical history, and physical examination. The inclusion criteria were as follows: presence of HCV infection, determined by HCV-RNA, various degrees of liver fibrosis estimated by Fibromax and age over 18 years. Patient exclusion criteria consisted of: co-infection with other hepatitis viruses, co-infection with HIV (human immunodeficiency virus), chronic alcohol consumption, history of hepatocellular carcinoma and age under 18 years. The therapeutic regimens used were: ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) and dasabuvir (DSV), ledipasvir/sofosbuvir (LDV/SOF) and sofosbuvir/velpatasvir, taking into account that the genotype predominance in the study population was 1b. The antiviral treatment was administered as per protocol: OBV/PTV/r 12.5 mg/75 mg/50 mg, two pills once a day and DSV 250 mg twice a day; LDV/SOF 90 mg/400 mg once daily and SOF/VEL 1 pill daily. The duration of treatment was 12 weeks for all treatments. All patients achieved SVR. Patients were followed from the initiation of antiviral therapy until one year after and

BMI, serum total cholesterol, triglycerides, blood glucose, glycosylated hemoglobin were monitored. The study group was divided into two arms according to the presence of diabetes (defined as glycosylated hemoglobin over 6.5%); thus group 1 was represented by 58 patients with CH-HCV and T2DM, and group 2 was represented by 42 CH-HCV patients without T2DM.

Statistical data processing

Statistical analysis was performed using SPSS version 23. Continuous variables were expressed as mean values ± standard deviation or median, categorical variables were represented as relative or absolute frequencies. Characteristics were compared using the Mann-Whitney method or the two-sample Student's T-test method for continuous variables, Chi-square and Fischer's test for categorical variables. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 100 patients were enrolled in the study and consisted of 43 males (43%) and 57 females (57%). Patients were evaluated at the initiation of antiviral treatment, then one year after initiation of antiviral therapy. At the initiation of antiviral treatment mean age was 63.22 years with a standard deviation of 9.1 years (Table 1).

Regardless of the presence or absence of diabetes, all 100 patients included in the study achieved SVR. No treatment-relevant adverse effects or drug interactions were reported.

Out of the total number of patients with diabetes, 27 (46.6%) cases followed only a dietary regime, compared to 31 (53.4%) cases with treatment as follows: treatment with oral antidiabetics (OAD) - 13 cases (22.4% of all cases with diabetes, insulin treatment -16 (27.59% of all cases with diabetes) and OAD + insulin - 2 cases (3.45% of the total).

Table 1. Demographic and laboratory data in the study population at initiation of antiviral treatment

Characteristics	Group I N = 58	Group II N=42	p value
Male gender (%)	27 (46.6%)	16 (38.1%)	0.399
Mean age (yrs) ± standard deviation	62.72 ± 9.49	63.9±8.6	0.525
Mean Cholesterol (mg/dL)	173.89 ±38.91	173.05±40.81	0.936
Mean triglycerides (mg/dL)	131.95 ± 47.22	131.81 ± 65.14	0.993
Median HbA1c (IQR)	6.56 (5.79, 7.07)	5.86 (5.43, 6.3)	0.004
Median blood glucose (mg/dL) (IQR)	141.5 (117.75, 176.5)	104.5 (96.5, 124)	<0.001

The values of serum total cholesterol and serum triglycerides are similar for the 2 groups of patients at the time of study initiation. The mean value of total cholesterol was 173.05 mg/dL for group 1 vs. 173.9 mg/dL for group 2 (p = 0,936) and that of triglycerides 131.95 mg/dL in group 1 vs. 131.85 mg/dL in group 2 (p = 0,993). The median blood glucose value at the time of inclusion in the study was 104.5mg/dL for group 2, respectively 141.5 mg/dL in group 1. Regarding glycosylated hemoglobin values, at the start of the study the median HbA1c in group 2 was 5.86%, while in the case of patients with diabetes the median HbA1c value was 6,56%.

Table 2. Demographic and laboratory data in the study population, 1 year after initiation of antiviral therapy

Characteristics	Group I N = 58	Group II N=42	p value
Mean age (yrs) ± standard deviation	63.72 ± 9.49	64.9 ± 8.6	0.525
Mean Cholesterol (mg/dL)	171.47 ± 42.54	204.43 ± 38.43	<0.001
Mean triglycerides (mg/dL)	116.27 ± 57.71	111.88 ± 52.38	0.731
Median HbA1c (IQR)	6.58 ± 1.15	5.81 ± 0.58	0.002
Median blood glucose (mg/dL) (IQR)	135 ± 44.69	105.15 ± 16.23	<0.001
Median blood glucose (mg/dL) (IQR)	141.5 (117.75, 176.5)	104.5 (96.5, 124)	<0.001

We observe that one year after initiation of DAAs the mean value of total serum cholesterol was significantly higher in group 2 (204 mg/dL vs. 171 mg/dL, p <0,001), whereas the mean value of triglycerides remains similar between the two groups one year after initiation (p = 0,731). The mean blood glucose value 1 year after initiation of antiviral treatment was 135 mg/dL for group 1, respectively 105 mg/dL for group 2. The mean values of glycosylated hemoglobin 1 year after initiation of treatment were 6.58% for patients with T2DM and 5.81% for patients without T2DM (Table 2).

Regarding the lipid profile, both groups showed an increase in total Cholesterol and triglycerides one year after completion of treatment (Table 3). Regarding total cholesterol the increase was higher in group 2 (8,88 mg/dL vs 7 mg/dL), but with no significant differences between the two groups (p = 0,215). Concerning the kinetics of triglycerides, we also observe an overall increase in the values, with a more important increase in group 2 (23 mg/dL vs 20 mg/dL), but with no significant differences (p = 0,836).

TABLE 3. Differences in lipid profile parameters at treatment initiation versus 1 year after treatment initiation

Characteristics	Group I N = 58	Group II N=42	p value
Δ Cholesterol (mg/dL)	-7 (-9.28, 43.69)	-8.88 (-35.96, 9.19)	0.215
Δ Triglycerides (mg/dL)	-20 (-51, -8)	-23 (-37, 0)	0.839

DISCUSSIONS

Following the analysis and comparison of the data obtained at the initiation of antiviral therapy and one year after treatment of the 2 groups of patients with HC-HCV, respectively the group of patients with T2DM and the group of patients without T2DM, the following aspects can be observed.

Serum lipids

At the beginning of the study the serum values of total cholesterol and triglycerides were similar, but one year after initiation the median value of serum total cholesterol was higher in the group of patients without T2DM respectively the median value of triglycerides one year after initiation of DAAs remains similar for the 2 groups of patients.

One of the hypotheses of the study took into account the persistence or even progression of serum cholesterol levels after curative anti-HCV therapy. The data from our study do not suggest that DAAs have a direct effect on increasing serum lipid levels and that viral suppression is responsible for worsening hyperlipidemia.

The values of the lipid parameters of the non-diabetic patients compared to the diabetic ones are consistent with the data in the literature, a significant increase in the total serum cholesterol values being observed one year after the initiation of treatment, especially due to the HDL fraction, but in the case of the group of patients who also associated T2DM, no significant increase was observed. Furthermore, in both groups of patients we observed an increase in serum triglycerides, but similar between the two groups.

The changes in the lipid profile could be explained by improving the effects of insulin, but also by the disappearance of the metabolic alterations associated with the viral infection, which leads to the maintenance of a constant concentration of total cholesterol. In the case of patients without diabetes, with virological cure, the lipid profile improves only on account of this aspect, the result being the increase of circulating lipids, especially on account of the HDL-Cholesterol fraction, results highlighted also in the case of the study conducted by Graf C et al [28] and Huang et al [29], which also concluded that these patients have a higher risk of cardiovascular disease.

Blood glucose and glycosylated hemoglobin

In the case of the group of patients with T2DM, contrary to most of the data in the literature no significant decrease is observed neither in the case of blood glucose values, nor in the case of glycosylated hemoglobin values one year after initiation of DAAs compared to the moment of initiation of the study. Regarding the values of glycosylated hemoglobin at the start of the study and one year after initiation of DAAs, they remain constant for both groups of patients.

Starting from the premise that in the era of DAAs emphasis is placed on outstanding or de novo changes that appear in patients who have obtained SVR, we can state that patients who associate HCV and diabetes behave differently from the point of view of the metabolic profile compared to patients without T2DM.

Regarding the evolution of the values of triglycerides, blood glucose and glycated hemoglobin, no significant differences were found between the 2 groups of patients. Both patients with diabetes and those without T2DM showed similar values of these markers, both at the beginning and one year after treatment.

The improvement of the quality of life and the psychological profile with the increase in appetite and sense of taste could be the explanation for the results obtained in the present study regarding the carbohydrate profile. Although insulin resistance improves, with the initial decrease in glycosylated hemoglobin, fasting glucose values and HOMA-IR after successful antiviral treatment, as stated also by Graf et al [28], Li et al [31], Abdo et al [34] returns to the initial values 1 year after treatment, sometimes even with the need to escalate antidiabetic therapy. Although the majority of studies conducted through the years support the idea of improving the carbohydrate profile, some studies concluded that there were no significant variations in serum glucose before and after cure of HCV Carvalho et al [8], or in glycosylated hemoglobin as stated by Doyle et al [32] and Stine et al [35]. The information underlined by these authors is consistent with the data findings in our study.

Decades of research have concluded that HCV must be considered further than liver infection. HCV causes multiple extrahepatic manifestations, among which the promotion of insulin resistance, but also the influence of lipid metabolism. Starting from these considerations, it is expected that with viral cure, both the carbohydrate profile and the lipid profile will improve. However, few studies on

metabolic changes have been performed, mainly due to the relatively recent introduction of effective direct antiviral therapy, which is why the data in the literature are relatively scarce and inconsistent.

In previous studies, it was proven that HCV infection causes insulin resistance. Therefore, the eradication of HCV infection should decrease insulin resistance. In the Virhep-C study [36], in patients treated with pegylated interferon who obtained SVR, an improvement in insulin resistance was observed 24 weeks after the completion of therapy. Furthermore, previous studies that analyzed insulin resistance in patients treated with direct antivirals did not reveal contradictory results. Carvalho et al. [8] studied direct antivirals and did not detect significant changes in terms of glycaemia values one year after therapy, but the degree of insulin resistance seems to have increased. In contradiction, a study carried out by Gitto et al. [33] demonstrated that the degree of insulin resistance decreased after direct antiviral therapy.

CONCLUSION

Regarding glucose metabolism our study found that there were no significant changes 1 year after treatment initiation in diabetic patients, contrary to what would be expected after viral clearance.

Moreover both diabetic and non-diabetic patients tend to have increased values in serum total cholesterol and triglycerides 1 year after treatment initiation, which would mean an overall worsening in lipid metabolism, with further risk of cardiovascular complications. However the present study did not take into account other factors that could influence lipid and glucose metabolism, like patients' lifestyle and improvement of quality of life, which could be responsible for these changes.

Despite previous discussions, the exact mechanism and long-term effects of HCV on lipid and carbohydrate metabolism require future studies.

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