RESEARCH NOTE

Rapid decline of fasting glucose in HCV diabetic patients treated with direct-acting antiviral agents

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Abstract

Association between hepatitis C virus (HCV) infection and diabetes has been widely postulated. Little is known about the effect of direct-acting antiviral agents (DAAs) on glycaemic control. The aim of our study was to evaluate the glycaemic control modifications in a case series of HCV-positive diabetic patients receiving DAAs. We retrospectively evaluated 149 HCV-positive patients in two different institutions affiliated with Sapienza University: Policlinico Umberto I of Rome and Ospedale Santa Maria Goretti of Latina. We were able to identify 29 patients with type 2 diabetes mellitus (19% of total population) who were receiving different interferon-free regimens. During-treatment fasting glucose (FG) values were available for 21 patients, and analysis revealed a statistically significant reduction (p 0.007); reduction mean value was −52.86 mg/dL. A glycated haemoglobin (A1C) value during treatment (at weeks 4, 8 and/or 12) was available for ten patients, and the analysis revealed a statistically significant reduction (p 0.021) with a reduction mean value of −1.95%. Six patients (23%) needed to reduce hypoglycaemic drugs, eight of ten patients showed reduction of A1C and 14 (67%) of 21 patients showed reduced FG during treatment. FG and A1C reductions values were independent from which DAA was present in the regimen, HCV genotype, body mass index and HIV status. In order to avoid hypoglycaemic events, diabetic patients receiving DAAs should be closely monitored for reduction of hypoglycaemic drugs. Furthermore, in our opinion, diabetes could be considered as an element to prioritize treatment in those patients with no apparent liver disease.

Introduction

Association between hepatitis C virus (HCV) infection and diabetes has been widely postulated. Prospective studies have demonstrated a higher risk of developing type 2 diabetes mellitus (T2DM) and insulin resistance in the HCV population, especially after liver transplantation [1–4]. Little is known about the effect of direct-acting antiviral agents (DAAs) on glycaemic control. To our knowledge, only a single case report has highlighted the possibility of hypoglycaemia during treatment [5]. The aim of our study was to evaluate the glycaemic control modifications in a case series of HCV-positive diabetic patients receiving DAAs.

Methods

We retrospectively evaluated 149 HCV-positive patients who had already completed or at least begun treatment for 1 month with interferon (IFN)-free regimens at two different institutions affiliated with Sapienza University: Policlinico Umberto I of Rome and Ospedale Santa Maria Goretti of Latina. We were able to identify 29 patients with T2DM (19% of the total population) who were receiving different IFN-free regimens including sofosbuvir + ribavirin (n = 8), sofosbuvir + simeprevir (n = 5), ledipasvir/sofosbuvir with or without ribavirin (n = 6), sofosbuvir + daclatasvir with or without ribavirin (n = 6) and ombitasvir/paritaprevir/ritonavir with or without dasabuvir and with or without ribavirin (n = 4). The mean age of the patients was 59.28 years (range 43–83 years); 24 were men and five were women, and all were Italian except for one patient from Egypt. The diabetes diagnosis followed the HCV diagnosis in 19

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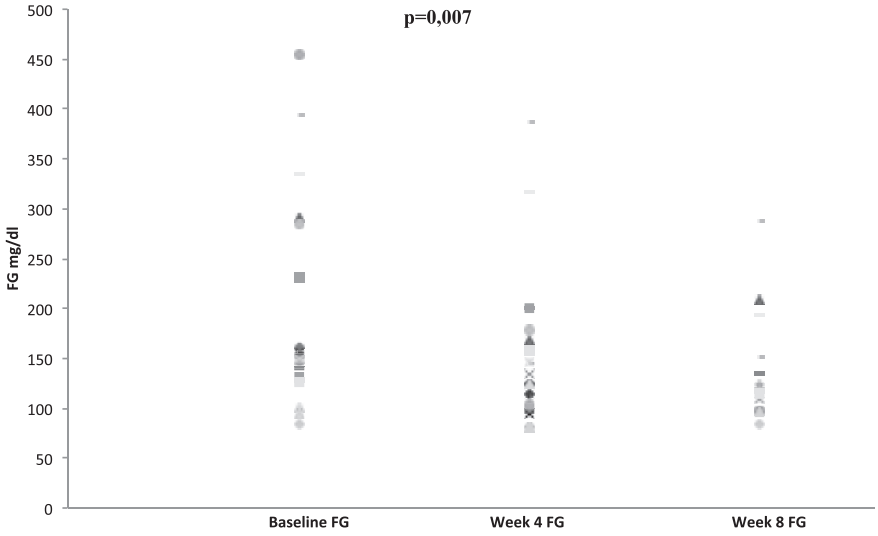

FIG. 1. Fasting glucose values at baseline, at week 4 and at week 8. The paired *t*-test showed a statistically significant reduction between baseline values and during-treatment values (p = 0.007).

patients and was a previous diagnosis in seven patients. In the remaining three patients, the year of diabetes diagnosis was not reported.

The HCV genotype distribution was as following: 1a genotype *n* = 7, 1b genotype *n* = 10, 1a/1b genotype *n* = 1, 2 genotype *n* = 4, 3 genotype *n* = 5 and 4 genotype *n* = 2. Fifteen of 29 patients had received IFN therapy, 20 presented advanced fibrosis/compensated cirrhosis (defined as liver stiffness >13 kPa) and four presented advanced liver disease (following the Child-Pugh B classification criteria). Ten patients were HIV positive, all with undetectable HIV RNA and $CD4^+$ cells >14%, with different highly active antiretroviral therapy (HAART) regimens (including one elite controller not receiving HAART). All the patients had HCV RNA undetectable at end of treatment or no more than 15 UI/mL at week 4 if still receiving treatment. All patients except one experienced normalized liver enzyme values at week 4. Analysis of fasting glucose (FG), glycated haemoglobin (A1C) and hypoglycaemic drug modification were independently prescribed by patients' reference diabetologists or family doctors. Nine patients were receiving metformin, 15 insulin and one repaglinide; four were not receiving any hypoglycaemic drug. We considered valid as pretreatment values only those recorded at baseline or within a maximum of 3 months before the start of DAAs. Using these criteria, pretreatment FG values were available for 27 patients; we found the mean value to be 175 mg/dL (minimum 85 mg/dL, maximum 455 mg/dL). Pretreatment A1C values were available for 17 patients, with a mean value of 7.1% (minimum 5.1%, maximum 11.8%).

To compare pretreatment and during-treatment values, paired *t* tests were performed by R software.

Results

During-treatment FG values were available for 21 patients (at weeks 4, 8 and/or 12). Analysis (using week 8 values when available or, alternatively, week 4) showed a statistically significant reduction (p 0.007) (Fig. 1), the reduction mean value was −52.86 mg/dL (with the maximum reduction observed of 357 mg/dL in a patient that switched from 455 to 98 mg/dL at week 8). An A1C value during treatment (weeks 4, 8 and/or 12) was available for ten patients. The analysis revealed a statistically significant reduction (p 0.021), with a reduction mean value of −1.95% (with the maximum reduction observed of 7.1% points in a patient who switched from 11.8% to 4.7% at week 8). To better evaluate the improvement of glycaemic control, we used a composite end point given by reduction of FG (of a minimum of 20 mg/dL) or A1C (of a minimum of 0.5%) or reduction of hypoglycaemic drugs dosing during anti-HCV treatment. Four patients were excluded from the analysis because data were insufficient (e.g. only one glycaemic value, no data on hypoglycaemic drugs, no way to make a comparison). The end point was reached by 21 (84%) of 25 patients. Six patients (23%) needed to reduce hypoglycaemic drugs (two patients reduced metformin dosing and four patients reduced insulin dosing). Eight of 10 patients showed reduction of A1C, and 14 (67%) of 21 patients showed reduced FG during treatment.

FG and A1C reductions values were independent of which DAA was present in the regimen, HCV genotype, body mass index and HIV status by Kruskal-Wallis test and the Welch one-way ANOVA procedure (R software). No cases of

symptomatic hypoglycaemia were found. In the four patients who did not reach the end point, three presented normal baseline FG (<110 mg/dL) and A1C (<6%) while receiving only metformin, so no significant reduction of glycaemic values was expected. The observation that patients with normal baseline FG and A1C did not experience hypoglycaemia suggests that the direct hypoglycaemic effect of DAAs or drug–drug interactions with insulin and metformin should be excluded. The remaining patient who did not experience improvement of glycaemic control had advanced liver disease (Child-Pugh B) and was the only patient with persisting elevated liver enzymes at the end of treatment. Unlike the other patients, he had worsening of FG values, leading to an increase in his insulin dose; he also experienced a retinal haemorrhage during treatment.

Discussion

The mechanisms by which HCV might induce diabetes represent a critical issue, especially in patients without cirrhosis. In fact, it can be presumed that in patients with advanced liver disease the insulin-signalling pathway is also altered by the presence of cirrhosis itself. In addition, it could be useful to classify patients with hepatogenous diabetes or hereditary T2DM to better define the effect of HCV eradication on these distinct situations [6], but this is not always possible because there is still no official definition of hepatogenous diabetes in international guidelines.

This retrospective evaluation of our diabetic HCV-positive population showed that HCV suppression after DAA treatment was associated with a marked decrease in FG values to below the normal cutoff after only 4 weeks of treatment. In order to avoid hypoglycaemic events, diabetic patients receiving DAAs should be closely monitored for reduction of hypoglycaemic drugs. Furthermore, diabetes could be considered as an element indicating the need to prioritize treatment in patients with no apparent liver disease. Prospective studies should be performed to better define the effect on insulin resistance of HCV suppression after treatment with the new DAAs.

Transparency Declaration

All authors report no conflicts of interest relevant to this article.

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