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Letter to the Editor

HCV and diabetes: towards a 'sustained' glycaemic improvement after treatment with DAAs?

We read with interest the paper by Pavone and colleagues [1] describing the rapid reduction of fasting glucose (FG) levels in diabetic hepatitis C virus (HCV)-positive patients receiving direct-acting antiviral agents (DAAs). In particular, FG decrease in course of treatment was described in 29 patients, leading to hypoglycaemic drug adjustment in six of them. Whether these changes represent a side effect due to drug–drug interactions or are a consequence of improved glycaemic control after achieving HCV viraemia suppression remains unclear.

We aimed to assess if a similar decreasing trend of FG levels occurred in our study population and if it was maintained after the end of treatment (EOT). Therefore, we retrospectively evaluated 449 patients treated with DAAs at our centre (64 HIV/HCV coinfected), who had reached EOT or who had initiated therapy since at least 4 weeks. Approval of the research ethics committee was not required because of the retrospective nature of the study, according to local regulations. We included all 59 subjects (13.1%) with type 2 diabetes mellitus. Median age was 68 years (range 48–86 years), and 40 were men (67.8%); the majority of patients (81.3%) had cirrhosis. HCV genotypes (gt) were distributed as follows: 1a gt $n = 6$; 1b gt $n = 29$; 2 gt $n = 15$; 3 gt $n = 5$; 4 gt $n = 4$. Nine subjects were HIV/HCV coinfected, all of whom were receiving effective antiretroviral therapy, with a median $CD4^+$ count of 486/μL (27%).

Antidiabetic treatment was based on insulin in 16 patients and on oral hypoglycaemic agents in 31 patients; two subjects assumed both insulin and hypoglycemic agents, and ten were not receiving treatment.

The following regimens were prescribed: sofosbuvir + ribavirin (RBV) in 19 patients (32.2%); sofosbuvir + simeprevir ± RBV in eight (13.5%); sofosbuvir/ledipasvir ± RBV in 15 (25.4%); ombitasvir/paritaprevir/ritonavir + dasabuvir ± RBV in 16 (27.1%); and sofosbuvir + daclatasvir + RBV in one (1.6%).

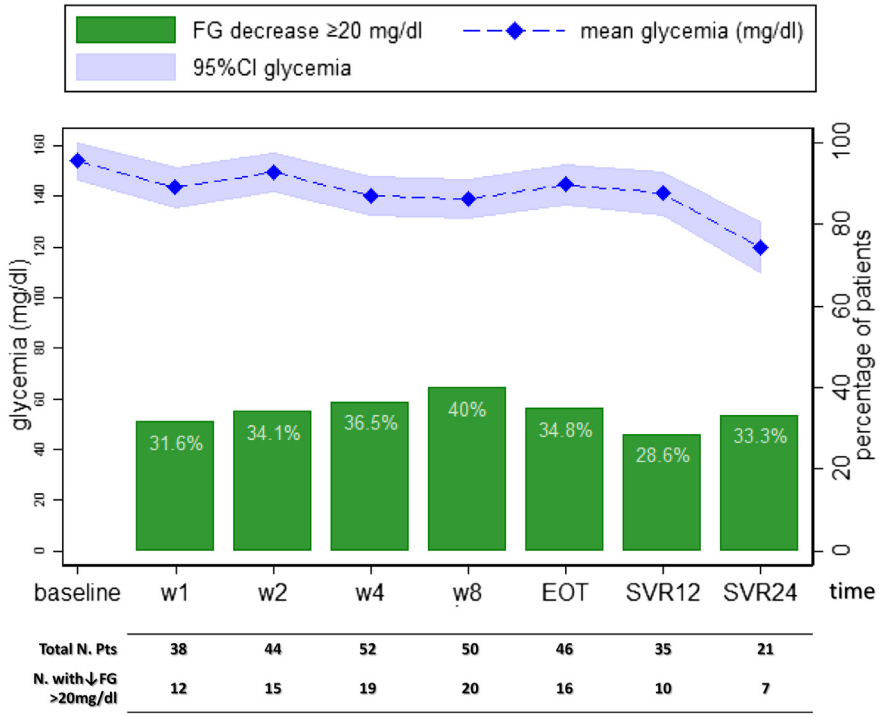

Fig. 1. Modification of fasting glucose (FG) levels during and after treatment. Dotted line shows trend of mean glycaemia levels. Bars represent percentage of patients with decrease of FG levels ≥20 mg/dL. Time points are expressed in weeks (w).

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Pretreatment FG values (mean 154 ± 52 mg/dL) within 3 months from therapy initiation and at least one FG value during treatment were available for all subjects. FG values at EOT (weeks 12 and 24) were obtained in 46 patients. Furthermore, FG levels were determined at weeks 12 and 24 after EOT for 35 and 21 patients, respectively. FG levels variations during treatment, and in addition a decrease of at least 20 mg/dL compared to baseline, were analysed using generalized mixed regression models.

A decline of mean FG levels was observed during treatment, and it was maintained both until the EOT and also in patients with 12 and 24 weeks' follow-up after EOT (Fig. 1). This decline was statistically significant at week 4 (p 0.023) and week 8 (p 0.017), with sustained virologic response at 24 weeks ($p < 0.001$).

However, FG decrease rarely was clinically significant. In fact, only one patient required an insulin reduction due to hypoglycaemia. Conversely, four patients experienced a worsening in glycaemic control (three during treatment and one after EOT), requiring, in two cases, antidiabetic treatment modification. Only three (8.9%) of 35 subjects did not experience sustained virologic response at 12 weeks; interestingly, in these patients, FG levels did not decrease.

In patients receiving antidiabetic treatment, a significant association with FG decrease >20 mg/dL was found (insulin, odds ratio 2.934, 95% confidence interval 1.137–7.575, p 0.02; oral antidiabetic drugs, odds ratio 1.576, 95% confidence interval 1.116–5.526, p 0.02). No correlation was detected with other variables (sex, age, body mass index, HIV coinfection, cirrhosis, grade of liver fibrosis), in agreement with Pavone and colleagues.

Although the correlation between chronic HCV and type 2 diabetes mellitus has been widely investigated [2,3], so far little is known about the impact of DAAs regimens on the diabetic HCV population, although cases of improved glycometabolic control after DAAs were recently reported [4]. On the basis of our results, these treatments seem to play a role in reducing FG levels, not only in course of therapy (as shown by Pavone and colleagues) but also after the EOT, suggesting that molecular pathways causing insulin resistance and alterations of glucose homeostasis [4] might be inhibited by the rapid suppression of HCV replication and of concurrent systemic inflammation. Therefore, the improvement in clinical course of type 2 diabetes mellitus previously described in literature with regards to interferon-based regimens [5,6] could be an expected, and perhaps earlier, effect of DAAs therapy as well. Larger prospective studies with a more complete baseline assessment and a prolonged follow-up would probably help clarify the complex mutual interactions between these two chronic systemic diseases.

Transparency Declaration

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