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The impact of a successful treatment of HCV on glyco-metabolic control in diabetic patients

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Dear Editor,

We read with interest the review by Adinolfi et al highlighting the need to evaluate all persons with Hepatitis C Virus (HCV) infection for diabetes, in view of extrahepatic benefits of viral eradication, the reduced risk of diabetic complications and improved glyco-metabolic control in HCV-infected patients [1]. Previous studies have shown that HCV impairs glucose metabolism directly via viral proteins and indirectly by altering pro-inflammatory cytokine levels [2–4]; thus, in turn, HCV clearance may positively impact on glucose metabolism, as evidenced by decreased mean haemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) levels [5,6] in diabetic patients exposed to new Direct Acting Antiviral (DAA) agents that produce a Sustained Virological Response (SVR) in nearly all cases. However, there are limited data on the effect of viral eradication with DAAs on established type 2 diabetes (T2DM) and whether the benefits are persistent [7,8].

In view of the clinical importance of the above issue, we assessed if a correlation between HCV eradication following DAA-based therapy and improvement in glyco-metabolic control occurred in our study population and if it was maintained after the end of treatment (EOT). We retrospectively compared HbA1c and FPG levels at baseline and post-SVR (at 12 weeks) in 93 patients with T2DM exposed to DAAs for HCV eradication (Figure 1 show the selection process of patients with HCV and diabetes enrolled in the study). To evaluate the glycometabolic response, we used a composite end-point given by the reduction of plasma glucose levels of at least 20 mg/dl (1.1 mmol/L) and a reduction of HbA1c of 0.5% compared to baseline values as a significant improvement in the glyco-metabolic response, as previously reported in some studies that addressed the issue [9,10].

As reported in Table 1, we found a significant post-SVR level reduction both of plasma glucose (P=0.0378) and HbA1c values (P=0.0039), as previously reported by four similar retrospective studies [5,9–11]. In contrast with our findings, no change in HbA1c was found 12-weeks post SVR by Stine et al among 26 HCV diabetic patients treated with SOF/LED (P=0.268) [12] and also Carvalho et al failed to identify maintained post-SVR benefits in terms of plasma glucose level reduction in patients without diabetes exposed to DAAs [8]. Furthermore, two previous studies found no significant difference in changes in HbA1c and glucose levels from baseline to the last follow-up in subjects who achieved SVR in a mixed cohort of
diabetic and non-diabetic patients [7,13]. These conflicting results may be in part attributable to the fact that our median HbA1c levels at baseline were higher (59.19±16.31 mmol/mol; 7.6%) than the ones reported in the studies mentioned before, suggesting that an improvement in glyco-metabolic response is more likely to occur in patients with established diabetes and with high baseline levels of HbA1c. In line with this hypothesis, as correctly reported by Adinolfi et al in their interesting review [1], Hum et al found drops in HbA1c associated with SVR restricted to diabetic patients with a high baseline HbA1c (mean HbA1c >7.2%), whereas among diabetic patients with pre-treatment HbA1c ≤7.2% there was no significant difference based on SVR [5].

A recent meta-analysis quantifying variations of glyco-metabolic indicators attributed to DAA therapy in diabetic patients detected a significant improvement in glyco-metabolic control after HCV eradication, in terms of HbA1c (-0.45%; P<0.001) and mean plasma glucose (-22.03 mg/dL; P=0.03) levels reduction, following DAA treatment in patients with established diabetes [14]. However, these promising findings came from a limited number of studies performed in a wide variety of clinical settings and need to be confirmed.

In conclusion, an increasing number of evidence seems to suggest that the eradication of HCV with DAA therapy may play a role in improving glycemic control in patients with established T2DM, highlighting the need to explore the issue through more wide-ranging studies, with a more complete baseline assessment and a prolonged follow-up, with a view to a possible tapering of anti-diabetic drugs in order to avoid hypoglycaemic events.

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Conflict of interest
The authors declare that there is no conflict of interest regarding the publication of this article

References


**Table 1.** Baseline demographics and effect of treatment of HCV with DAAs on glyco-metabolic parameters

| Baseline demographics for HCV patients with diabetes with pre-and post-treatment laboratory values |
| Age (years), mean±SD | 64±11 | - | - |
| Male, gender, n (%) | 72 (73%) | - | - |
| Genotype, n (%) | 47 (55.9%) | 18 (21.4%) | - | - |
| 2 | 13 (15.4%) | - | - |
| 4 | 8 (9.5%) | - | - |
| not performed | 9 (10.7%) | - | - |

**Changes in laboratory values**

<table>
<thead>
<tr>
<th></th>
<th>Before [mean ± SD]</th>
<th>After [mean ± SD]</th>
<th><em>P</em> value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean plasma glucose levels, mg/dL</td>
<td>166.9±50.63</td>
<td>149.9±49.53</td>
<td><strong>0.0378</strong></td>
</tr>
<tr>
<td>Hemoglobin A1c, mmol/mol</td>
<td>59.19±16.31</td>
<td>49.81±16.25</td>
<td><strong>0.0039</strong></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>164.2±35.13</td>
<td>182.4±38.54</td>
<td><strong>0.0010</strong></td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>186.3±83.27</td>
<td>173.9±101.6</td>
<td>0.5268</td>
</tr>
</tbody>
</table>

SD: standard deviation; HCV: Hepatitis C Virus; DDA: Direct Acting Antiviral.
* Statistical significance assessed by paired Student’s t-test. *P* values < 0.05 were considered statistically significant.
**Figure 1.** Selection process of patients with HCV and diabetes enrolled in the study

Number of screened patients with DAA therapy

- **1198**

Number of HCV/diabetics patients

- **99**

Patients with complete blood glycemia values

- **67**

Patients with complete glycated hemoglobin values and glycemia

- **23**

Patients with complete glycated hemoglobin values

- **26**