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LETTER TO THE EDITOR

Systemic adipokines, hepatokines and interleukin-6 in HCV-monoinfected and HCV/HIV coinfected patients treated with direct antiviral agents (DAAs)

KEYWORDS
HCV;
DAAs;
Diabetes;
Hepatokines;
Adipokines;
Cytokines

To the Editor,

The introduction in clinical practice of the new direct-acting antiviral agents (DAAs) has induced dramatic advances in the management of chronic HCV infection [1]. Recent reports demonstrated that DAAs were associated with a rapid improvement of fasting glucose (FG) and glycated haemoglobin (HbA1c) values in diabetic HCV-infected patients during treatment [2]. The underlying mechanism of these clinical observations has not yet been elucidated. Here, the circulating levels of proteins related to IR such as adiponectin (ADPN), selenoprotein P (SelP), fetuin A (FetA), and the cytokine interleukin-6 (IL-6) were assessed in HCV-infected patients receiving an interferon-free regimen.

The study population included 31 patients with active HCV infection, 16 were HIV/HCV co-infected and 15 were HCV mono-infected. Among this population, we were able to identify 14 diabetic and 17 non-diabetic patients. The median age of diabetic and non-diabetic patients was 61 and 54 years, respectively. Most patients were male (79% of diabetics, 59% of non-diabetics). The most frequent genotype was genotype 1. Many patients had severe or advanced fibrosis (100% of diabetics, 71% of non-diabetics). All HIV positive patients had undetectable HIV-RNA (< 50 copies/mL) and all but one (elite controller) were treated with different antiretroviral regimens. Among the diabetic patients, three were receiving metformin, six were receiving insulin, one repaglinide and four patients were not receiving treatment for T2DM. The patients were treated with interferon-free DAAs according to the European Guidelines for HCV treatment at the time of enrolment (year 2015). In diabetic patients, we assessed FG and HbA1c values at baseline and at the end of treatment (EOT).

Blood samples were collected from each patient at baseline and at the EOT. Commercially available ELISA were used for the quantitative detection of plasma levels of SelP (Elabscience Biotechnology Co., USA), ADPN, FetA and IL-6 (Quantikine, R&D Systems, Minneapolis, MN), according to the manufacturer's instructions. A statistical analysis was performed using Prism Software 7. We used Wilcoxon test for paired samples, Mann–Withney test for non-paired samples. We also performed Pearson's correlation coefficient for parametric analyses and Spearman's correlation coefficient for non-parametric analyses. Results were expressed as median values and interquartile range (IQR). The study was approved by the local institutional review board. All study participants signed an informed written consent at the time of inclusion.

At the EOT, all patients had undetectable HCV-RNA and ALT values within the normal range. Baseline FG median value (MV) was 139 mg/dell (IQR = 86 mg/dL), EOT FG median value was 118 mg/dL (IQR = 52 mg/dL). Baseline HbA1c MV was 6.90% (IQR = 1%), EOT HbA1c MV was 6.80% (IQR = 2.35%). At the EOT, FG MV was reduced ($P = 0.006$), whereas a non-significant reduction of HbA1c was observed.

The levels of biomarkers before and at the end of treatment are reported in Fig. 1. The ADPN MV at baseline in the 31 HCV-infected patients was 6.11 μg/mL, IQR = 6.76 μg/mL and a significant reduction ($P = 0.005$) was observed at the EOT (4.85 μg/mL, IQR = 4.52 μg/mL). Likewise, for ADPN, SelP plasma levels were also significantly reduced at the EOT (baseline MV = 20.18 μg/mL, IQR = 47.01 μg/mL; EOT MV = 11.43 μg/mL, IQR = 9.39 μg/mL; $P = 0.0011$). We did not observe any significant variation of FetA and IL-6 plasma levels during DAA treatment in the study population.

The levels of biomarkers according to the presence of diabetes and HIV coinfected are displayed in Table 1. A statistical significant reduction of FetA was observed in HIV-negative patients (baseline MV = 2.49 mg/mL, IQR = 1.87 mg/mL, EOT MV = 1.06 mg/mL, IQR = 1.05 mg/mL, $P = 0.02$), whereas no significant variations were found in

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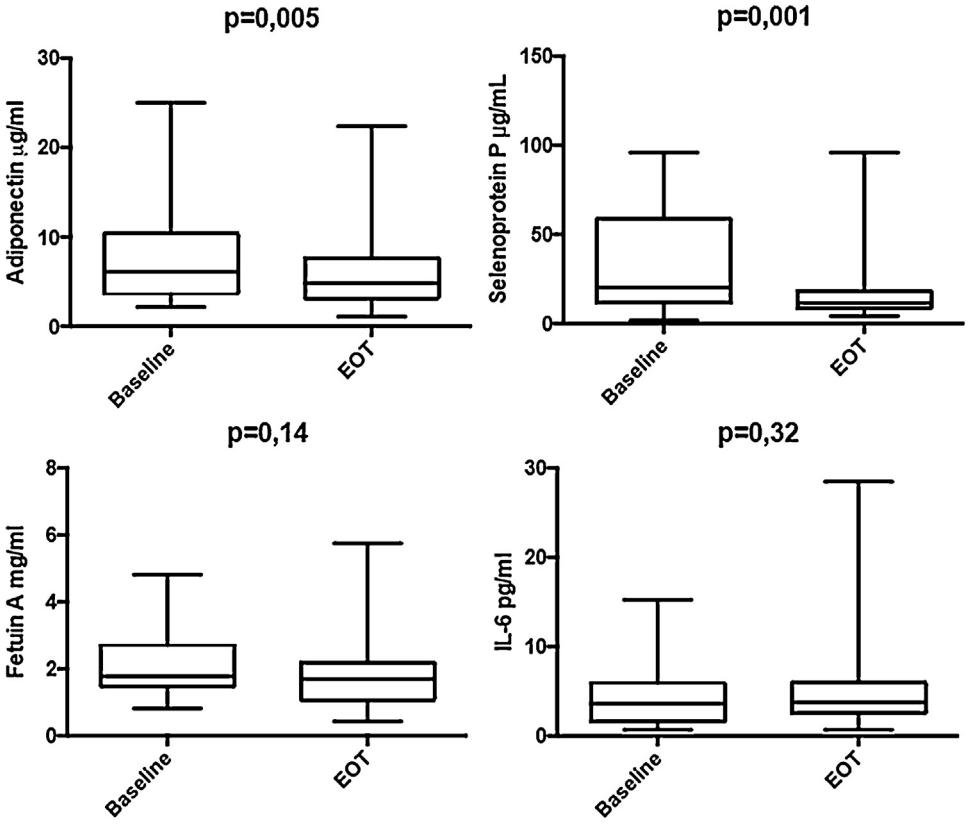

Figure 1 Circulating levels of ADPN, SelP, FetA and IL-6 in 31 HCV-infected patients. Plasma levels of ADPN, SelP, FetA and IL-6 were measured at baseline and end of treatment (EOT) with DAAs. A significant reduction was observed for ADPN and SelP.

HIV/HCV coinfected patients. IL-6 median values were significantly higher in co-infected than in mono-infected patients, at baseline (MV HIV-positive = 5.02 pg/mL, MV HIV-negative = 1.78 pg/mL, $P = 0.0071$) and at EOT (MV HIV-positive = 4.74 pg/mL, MV HIV-negative = 2.29 pg/mL, $P = 0.015$).

ADPN levels were significantly higher in women than men, both at baseline (MV in women = 12.52 μg/mL, MV in men = 5.39 μg/mL, $P = 0.035$) and at the EOT (MV in women = 10.55 μg/mL, MV in men 3.72 μg/mL, $P = 0.025$). We also noted that the reduction of SelP was greater in women (baseline MV = 23.69 μg/mL, IQR = 23.19 μg/mL, EOT MV = 11.43 μg/mL, IQR = 8.83 μg/mL; $P = 0.0195$) than in men. Finally, we found that baseline ADPN values were positively correlated with ALT levels (Spearman correlation test, $\rho = 0.60$, $P = 0.0008$) and HbA1c values (Spearman correlation test, $\rho = 0.75$, $P = 0.066$).

In the present study, we demonstrated that DAA treatment leads to modification of ADPN, SelP and FetA plasma levels in HCV-infected patients. ADPN improves insulin sensitivity in several tissues and has a negative correlation with markers of IR [3]. In our study, we observed a reduction of ADPN plasma levels at the EOT, compared to baseline values. In addition, we found a correlation between baseline ADPN plasma concentrations and ALT values, a marker of liver disease and a positive association between ADPN plasma levels and HbA1c values at baseline. These results could be considered paradoxical, but our findings are in accordance to a previous study performed in a population of HCV-infected patients treated with IFN-α, showing a decrease of serum ADPN levels and an improvement of IR in responders to the treatment [4]. We believe that the decrease of ADPN after antiviral treatment could be partially explained by the influence of hepatic inflammation on ADPN concentrations [5].

Higher FetA and SelP plasma levels have been associated to IR and impaired glucose homeostasis [6,7]. Sahar et al. have recently showed that FetA serum levels are higher in diabetic and non-diabetic HCV positive patients compared to healthy population and that SelP serum levels are higher in diabetic HCV positive patients compared to controls. The same study revealed an association between FetA and SelP levels and FG, and a correlation between FetA levels and HOMA-IR [8]. In our study we observed a decline of SelP plasma levels in HCV-positive patients treated with DAAs. A reduction of FetA was observed in HCV mono-infected patients. FetA is a negative acute phase reactant but it may induce low grade inflammation, thus having pro- and anti- inflammatory properties [7]. Our results in HIV/HCV coinfected patients could be explained by the inflammatory state related to HIV infection. IL-6 promotes IR and it has been related to the risk of development of T2DM. Furthermore, HCV-infected patients have higher IL-6 levels, compared to the healthy population [9]. Our study did not show a significant modification of this cytokine after HCV treatment. It should be underlined that IL-6 levels could be influenced by HIV infection [10] and that 16 of 31 (52%) patients were HIV-positive. Interestingly, an HIV-positive patient with decompensated diabetes had a wide

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Table 1 Adiponectin, selenoprotein P, fetuin A and interleukin-6 plasma levels at baseline and end of HCV DAA treatment according to the presence of diabetes and HIV coinfection.

	Diabetes		*P*-value	Non-diabetes		*P*-value	HIV+		*P*-value	HIV−		*P*-value
	Baseline	EOT		Baseline	EOT		Baseline	EOT		Baseline	EOT	
ADPN(μg/mL)	6.81 (5)	4.64 (3.98)	0.03	5.39 (10.62)	4.85 (10.65)	0.11	5.28 (11.52)	4.29 (9.11)	0.10	6.91 (4.17)	4.98 (3.5)	0.03
SelP (μg/mL)	17.21(50.99)	9.88(10.23)	0.09	26.84(57.49)	11.53 (10.18)	0.005	18.12(23.98)	11.64(10.92)	0.17	24.19(81.12)	10.90(8.01)	0.0012
FetA (mg/mL)	1.78 (1.91)	1.25 (1.11)	0.28	1.77 (1.09)	1.86 (1.11)	0.35	1.63 (0.85)	1.88 (0.62)	0.44	2.49 (1.87)	1.06 (1.05)	0.02
IL-6 (pg/mL)	2.95 (5.94)	3.4 (2.82)	0.73	4.26 (3.91)	4.18 (4.65)	0.55	5.02 (5.43)	4.74 (6.90)	0.53	1.78 (2.79)	3.00 (1.78)	0.64

Results are expressed as median (Interquartile range); EOT: end of treatment; ADPN: adiponectin; SelP: selenoprotein P; FetA: fetuin A; IL-6: interleukin-6.

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reduction of IL-6 levels (from 15.26 pg/mL to 3.66 pg/mL) and a wide reduction of HbA1c (from 10.4% to 5.9%), whereas SelP was increased at the EOT and FetA and ADPN were unchanged. In this patient it's plausible that inflammation had a key role in inducing the HCV-related IR.

All together these results suggest that altered levels of adipokines/hepatokines in HCV infection can be restored by DAA treatment, thus indicating the important metabolic changes occurring during the eradication of this viral infection.

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Disclosure of interest

The authors declare that they have no competing interest.

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