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LETTER TO THE EDITOR

Kinetics of serum hepcidin and interleukin-6 levels following COVID-19 infection in hemodialysis patients

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Patients with chronic kidney disease (CKD), particularly those undergoing hemodialysis (HD), are at high risk of a severe form of coronavirus disease 2019 (COVID-19). Recently we showed that an elevated neutrophil: lymphocyte ratio at day 7 of COVID-19 predicted outcome in adult HD patients [1]. Elevated serum C reactive protein (CRP) and ferritin were also hallmarks of the disease, confirming that, similar to all COVID-19 patients, hyperinflammation and iron disorder are also present in HD patients [2]. Here we additionally explored hepcidin, the master regulator of iron homeostasis that has rarely been measured in COVID-19 and interleukin-6 (IL-6), the cytokine that stimulates hepcidin in inflammatory conditions [3].

The study included 12 consecutive HD patients with confirmed COVID-19 recruited in one dialysis unit from Association pour l'Utilisation du Rein Artificiel between March and October 2020 (Supplementary files). Demographic characteristics at baseline are shown in Supplementary data, Table S1. All patients received monthly similar doses of intravenous iron or erythropoietin-stimulating agent (ESA) for anemia management (Supplementary data, Table S1).

The median age was 62 years (range 40–70), 33% were women and most were Caucasian (58%). Diabetes was observed in five patients. The median HD vintage was 76 months (range 18–120). Two-thirds of HD patients had severe COVID-19 (Supplementary files), with two patients requiring intensive care admission.

Hepcidin and IL-6 were measured at days 7, 14 and 90 after the infection (Supplementary files). Until day 14, both circulating IL-6 and hepcidin levels were significantly higher compared with

normal ranges (referenced as <7 pg/mL and <20 ng/mL for IL-6 and hepcidin, respectively). The IL-6 concentration increased from 12.4 pg/mL [interquartile range (IQR) 6.1–19.9] on day 7 to 43.3 pg/mL (IQR 3.3–49) on day 14 (Figure 1). However, hepcidin was already increased on day 7 [51 ng/mL (IQR 33–74)] and its median level remained stable on day 14 [62 ng/mL (IQR 39–97)].

There was a significant positive correlation between IL-6 and CRP. However, there was no correlation of hepcidin levels compared with those of ferritin, IL-6 or neutrophil count (Supplementary data, Figure S1). On day 90 post-infection, the levels of IL-6 and hepcidin decreased dramatically (Figure 1).

Since it has been reported that hepcidin predicts mortality in COVID-19 patients [4], we aimed to see if hepcidin was associated with the severity of COVID-19. Patients with a severe form had a similar median hepcidin concentration as compared with non-severe patients either at day 7 [61 ng/mL (IQR 44–74) versus 38 ng/mL (IQR 25–64); $P = 0.4$] or at day 14 [78 ng/mL (IQR 35–88) versus 46 ng/mL (IQR 43–85); $P = 1.00$].

Overall, in this small population of HD patients, we showed that IL-6 and hepcidin increased early in the period of COVID-19 infection but their levels were restored after the recovery period.

Surprisingly, hepcidin concentration did not correlate with ferritin concentration as described in CKD patients [4], suggesting possible dissociation between serum hepcidin and ferritin in COVID-19. The dissociation cannot be explained by the iron supplementation or the ESA dose, which were similar between both groups, but suggests an independent mechanism [5]. One hypothesis could be explained by a discrepancy in the rate and

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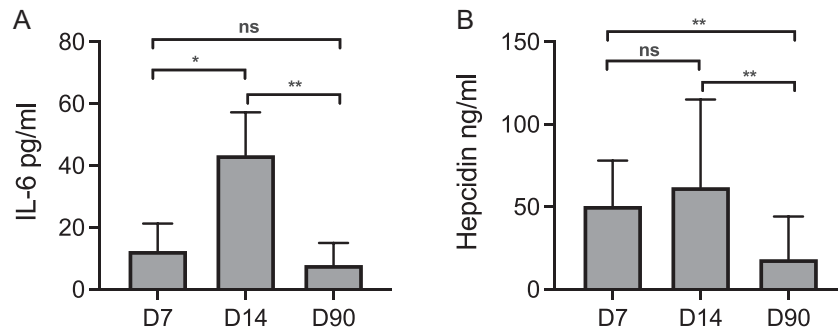


FIGURE 1: (A) IL-6 and (B) hepcidin kinetics in 12 HD patients at day 7 (D7), 14 (D14) and 90 (D90) after the COVID-19 diagnosis. Data are expressed as median and IQR. *P < 0.05, **P < 0.01. ns: non-significant (Mann-Whitney test).

production site of these two proteins in this peculiar context. Indeed, hepcidin is produced predominantly by hepatocytes while ferritin is ubiquitous and predominately produced by reticulo-endothelial cells that are highly active in response to infection. Thus the cytokine storm observed in COVID-19 may trigger ferritin rather than liver hepcidin. Ferritin was shown to be highly sensitive to COVID-19 conditions, with significantly higher levels in the severe form [3].

In conclusion, COVID-19 triggers ferritin and hepcidin differently in COVID-19 HD patients. Further studies are needed to investigate the prognosis value of hepcidin in HD patients.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

CONFLICT OF INTEREST STATEMENT

Pablo Ureña-Torres is a member of the CKJ editorial board. The other authors declare no conflicts of interest.

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