LETTER TO THE EDITOR

Reply to Jakovac: COVID-19, vitamin D, and type I interferon

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TO THE EDITOR: We read with great interest the letter of Jakovac (3) on vitamin D and coronavirus disease (COVID-19). The author critically extrapolated to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection existing data on the protective activity of vitamin D in the context of other viral infections. As an additional topic on this theme, we propose that vitamin D may cooperate with type I interferons (IFNs) to control the early phase of SARS-CoV-2 infection. Type I IFNs are the most powerful natural mediators of antiviral activity in humans, and there is growing evidence that a weak or delayed type I IFN response contributes to COVID-19 severity (6). Here, we briefly summarize literature data supporting the concept that vitamin D may cooperate with type I IFN to enhance antiviral responses.

Vitamin D has a direct antiviral effect against hepatitis C virus (HCV). It enhances IFN-α-mediated inhibition of HCV replication by increasing IFN-stimulated genes (ISGs) induction (2, 4). Interestingly, the combined treatment of infected human hepatocytes with low IFN-α and vitamin D concentrations, which separately have extremely weak antiviral effect, inhibited viral production. This synergism suggests that vitamin D potentiates IFN-α action (3). Moreover, a mechanistic study (4) described a constitutive inhibitory interaction between vitamin D receptor (VDR) and STAT1. This latter was, however, released upon stimulation with calcitriol, the biologically active form of vitamin D, suggesting that ligand-unbound VDR may sequester STAT1, a key transcription factor in type I IFN signaling. Thus, vitamin D deficiency could contribute to a less efficient IFN-mediated antiviral response due to higher levels of unbound VDR.

Vitamin D was shown to exert antiviral activity against rhinoviruses (8). In human tracheobronchial epithelial cells, it decreased rhinovirus replication and release, induced the antimicrobial peptide cathelicidin, and increased virus-induced expression of antiviral ISGs.

Evidence supporting an additive effect of vitamin D and IFN-β on the transcriptional induction of ISGs has come from in vitro and ex vivo studies on peripheral blood cells of patients with multiple sclerosis (MS) (1, 5). Munger and colleagues (5) aimed to correlate vitamin D status, disease activity, and global gene expression profiles over a course of up to 2 yr in patients starting treatment with IFN-β after a clinically isolated syndrome. The vitamin D effects on MS activity were additively enhanced by IFN-β. Of note, within the complex network of genes regulated by vitamin D, they found known targets of IFN-β, including antiviral genes.

Last but not least, both vitamin D (9) and type I IFN (10) may upregulate ACE2, the renin-angiotensin system component exploited by SARS-CoV-2 as cellular receptor.

Based on the above considerations, we put forward the hypothesis that an adequate vitamin D status at the moment of infection helps the early type I IFN protective response, and reinforces innate antiviral immunity to Sars-CoV-2. As disease progresses, vitamin D immunomodulatory activity might instead help reducing hyperinflammatory damages observed in severe COVID-19, justifying its use as an adjuvant therapy (3, 7). We believe that the still underexplored link between vitamin D status, type I IFN response, and COVID-19 outcome further underlines the importance of preventing vitamin D deficiency as a public health measure in the fight against the COVID-19 pandemic.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.C.G. drafted manuscript; M.C.G. and L.F. edited and revised manuscript; M.C.G. and L.F. approved final version of manuscript.

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