Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Letter to the Editor in response to article: Hypocalcemia is associated with severe COVID-19: A systematic review and meta-analysis (Martha et al.)

Keywords:
Hypocalcemia
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Intracellular calcium
Endoplasmic reticulum
Virus replication

Dear Sir,

We read the meta-analysis by Martha and colleagues reporting hypocalcemia as a predictor of poor outcome in patients with COVID-19 [1]. There are some caveats that obscure the results of studies examining the impact of serum calcium on COVID-19 severity. Most of them focus on the circulating levels of total calcium, while very few correct calcium to the concentration of albumin [2]. To further dispute the predictive value of total serum calcium, there are publications relating hypocalcemia with COVID-19 of only mild severity [3], whereas the most severe cases displayed hypercalcemia [4]. Targeting the total serum calcium, significant parameters of calcium homeostasis regulating the intracellular life of coronavirus are overlooked. It is known that total calcium represents a sum of three components: 45% protein-bound, 15% complexed to anions and 40% free or ionized calcium Ca^{2+}. This free Ca^{2+} is the biologically active component that mediates the intracellular homeostasis of calcium and determines the viral damage on host cells.

In order to ensure their intracellular life cycle, coronaviruses activate specific calcium channels on the plasma membrane as well as the endoplasmic reticulum, to increase Ca^{2+}, that favors viral internalization, replication and budding of virions [5]. Low levels of serum calcium, defined by hypocalcemia, are not able to block these efforts of coronaviruses to increase the intracellular Ca^{2+}, given that a small percentage of extracellular calcium contributes to the amount of cytoplasmic Ca^{2+}. The main buffer of intracellular Ca^{2+} is the endoplasmic reticulum which through its organelle membranes maintains the Ca^{2+} supply, even in case of hypocalcemia [6]. The intracellular transduction pathways signaled by Ca^{2+} are important for coronavirus survival and represent therapeutic targets of various evolutionary drugs, including calcium channel blockers, cardiac glycosides, thapsigargin and colchicine [7,8].

None of the above pharmaceutical substances are related to serum calcium levels. Besides, it is the Ca^{2+} mediated intracellular machinery that offers an explanation for hypocalcemia encountered in some COVID-19 infections. Serum calcium depletion constitutes a host's attempt to prevent coronavirus from creating an intracellular Ca^{2+} storm. Whether hosts fall victims themselves to this over-reaction, is unpredictable.

In conclusion, the meta-analysis by Martha and colleagues, supports a fundamental question: Is hypocalcemia of COVID-19 an independent cause of severity, or is it a mere bystander? To shed light to this scenario, a holistic re approach of hypocalcemia is warranted, based on both the extracellular and intracellular calcium metabolism.

Author declaration

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