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.

Nutrition, Metabolism & Cardiovascular Diseases (2020) **30**, 1401–1407

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

LETTERS TO THE EDITOR

Systemic endothelial dysfunction: A common pathway for COVID-19, cardiovascular and metabolic diseases

Dear Editor,

Amidst the pandemic that has mesmerized the entire world, as it has not spared anyone according to any specific characteristic, some conditions have in fact emerged as risk factors for a complicated evolution of COVID-19. Cardiovascular and metabolic diseases, including hypertension and diabetes, have been associated with more severe presentations and/or adverse prognosis [1].

As Li et al. point out in their recent paper [2], there is a complex network of predisposing factors in patients with cardiovascular disease. However, an important player in the scenario of cardiovascular and metabolic diseases was overlooked. Endothelial dysfunction – the impairment of the ability of the endothelium to maintain vascular homeostasis – is the final common pathway for diabetes/insulin resistance, hypertension, and dyslipidemia. The inflammatory state, increased oxidative stress, altered nitric oxide bioavailability, and insulin resistance are key factors of endothelial dysfunction [3,4]. Additionally, as SARS-CoV-2 infects host cells by means of the transmembrane angiotensin-converting enzyme (ACE)-II receptor, which is expressed in endothelial cells, there is substrate for a direct pathogenic effect of the virus [5]. Other noxious influences over the endothelium include effects of proinflammatory cytokines ("cytokine storm"), resulting in vascular endothelial cell apoptosis and leading to lung microvascular dysfunction, vascular leakage, alveolar edema, and ultimately hypoxia. Moreover, proinflammatory cytokines increase the expression of adhesion molecules, resulting in endothelial activation, procoagulant and proadhesive changes, worsening microvascular flow and, consequently, tissue perfusion. Pulmonary endothelial activation has been recently demonstrated in an autopsy study of 10 patients with COVID-19. Histological findings revealed exudative/proliferative diffuse alveolar damage, but endothelial tumefaction in pulmonary capillaries and fibrinous thrombi in small pulmonary arterioles were also found [6].

The chronic impairment of systemic endothelial function in patients with cardiovascular and metabolic disorders, when aggravated by the acute, noxious effects of SARS-CoV-2 over the endothelium, may explain their worse outcomes in COVID-19. Therefore, the recognition of the role of endothelial dysfunction in the pathophysiology of COVID-19 in patients with cardiometabolic disorders is relevant, and may offer a new target for therapies aiming at minimizing the severity of the infection in this patient population.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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5 May 2020

Handling Editor: A. Siani

https://doi.org/10.1016/j.numecd.2020.05.007

Comment on the systematic review: "Effects of zinc supplementation on lipid profile in patients with type 2 diabetes mellitus"

Dear editor,

We read with interest the work done by Asbaghi et al. [1], who comprehensively summarized the available evidence on the effects of zinc supplementation on different metabolic parameters of type 2 diabetes mellitus patients. We compliment the authors for this review article, on such an important subject for diabetic patients' healthcare. However, we would like to highlight a few analytical aspects regarding the interpretability of the presented results.

Our first concern relates to the extent to which the risk of bias assessment was described. Reporting the rationale on which judgments of risk of bias are based provides greater transparency and allows readers to decide whether they agree with the judgements made [2], an approach encouraged by the Cochrane Collaboration. This is important, since risk of bias often threatens the validity of individual studies' and meta-analyses' results alike.

In this sense, we point out to our second concern: most of the pooled estimates are substantially heterogeneous. Handling between-study heterogeneity was accordingly attempted by the authors through subgroup analyses, but readers are still left with an extensively unexplained variability in results across outcomes even after such investigations. However, none of the subgroup analyses considered the risk of bias assessments as a source of heterogeneity, despite being a highly recommended approach [3].

Moreover, subgroup analyses presented by the authors were not accurately prespecified with regards to direction of effect, which decreases the credibility of any apparent subgroup result. In addition, a large number of hypotheses testing leads to a multiple comparisons problem [4]. In this review, 48 different hypothesis tests were performed as subgroup analysis, which skyrockets the probability of type I errors. Following Boole's inequality from probability theory, there is a $1 - (1-0.05)^{48} * 100 = 91{,}47\%$ probability of a false-positive. It has been empirically shown that multiple post-hoc analyses often result in spurious and potentially misleading findings [5], especially due to their observational nature and the fact that they're not based on randomized comparisons.

Taken together, we do not believe our concerns dismiss the credibility of the current work. Rather, we draw attention to the interpretation of the presented results in relation to how much confidence the review users have in the estimates of effect, considering the previously emphasized concepts of inconsistency and certainty in the evidence, as well as the credibility of subgroup claims.

Funding sources

None of the authors have received any financial support.

Authors contribution

ICE and MLLI conceived the letter, which was discussed with and edited by AC.

Declaration of Competing Interest

The authors declare no conflict of interest.

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