Micronutrient deficiencies in patients with COVID-19: how metabolomics can contribute to their prevention and replenishment

Dear Editors,

Reading the recent article by McAuliffe *et al*,[1] we were interested in the approach presented to target the micronutrient deficiencies of the high-risk population for COVID-19 and empower their immune system against the infection.[1] The authors present evidence on the central role of selected nutrients on the immune system function against respiratory infections while showing clinical data from studies using prophylactic supplementation.

However, clinical studies have not yielded conclusive results on the beneficial role of nutrient supplementation to the support of the immune system that can be translated into clinical practice. The authors report three main reasons that we will elaborate on in this letter: (1) poor study design; (2) lack of an established methodology for the assessment of the micronutrient status; and (3) unstandardised optimal dosing of the nutritional supplements.

Clinical studies are usually designed to assess the role of a single nutrient on the immune system function. Although this approach facilitates close monitoring of the nutrient subtraction/supplementation effect, it does not reflect the biological system complexity. Thus, several interventional studies report no effect of the nutrient supplementation, which contradicts others that demonstrate a positive impact, hampering the validation of results.[2] It should also be noted that the primary role of nutrients, which is the facilitation of enzymatic reactions, is accomplished via the synergy of multiple nutrients. Thus, a combination of nutrients should be given as intervention instead of single nutrients.[3] In addition, a nutrient cocktail could be provided at baseline to cover some of the deficiencies permitting the normal function of metabolic pathways, prior to the administration of a single nutrient in a dose–response manner to assess its effect on health and disease. A control group receiving the nutrient cocktail should also be included in these studies in addition to the no-intake control group. Such study design might also reduce the interindividual differences in response to the intervention, caused by the diverse nutrient requirements within the sample population.

We propose both for human research studies but also for clinical practitioners to shift from single-nutrients assessment to the profiling of multiple nutrients at a given time for each person to have an overview of the micronutrient status and monitor the treatment efficacy. An obstacle towards this direction is that nutrients have markedly different chemical properties requiring other methodological handles for their assessment in human biofluids. To overcome this complexity, we propose an analysis of the metabolic products of nutrients in line with others.[4]

Recent evidence suggests that metabolomics could be an adjunct tool of identifying people with micronutrient deficiencies, and thus a high risk for COVID-19, and as a tool of monitoring progress after nutritional supplementation.

Metabolomics has attracted the attention of health researchers because it is a sensitive method able to capture metabolic dysfunctions caused by or predicting the presence of a disease.[5] Their unique advantage is that it combines the genetic variability of a person and the individual dietary and lifestyle preferences that affect the phenotype, which is metabolites. Significant progress has been made for the identification of metabolic biomarkers in chronic diseases,[6] though the application of metabolomics as a tool of nutritional deficiency assessment is limited to few nutrients. Targeted metabolomics, which provides the absolute quantification of metabolites, can capture the functional adequacy of nutrients by measuring the metabolic intermediates of enzymatic reactions regulated by the nutrients. For example, methylmalonic acid, a metabolite produced by methylmalonyl-CoA regulated by the bioavailability of B12, has been established in clinical practice. It requires a multidisciplinary approach, including nutritionists, biologists, biochemists, biostatisticians and physicians, to implement metabolomics into clinical practice.[7]

Lastly, it is important to note that the optimal dosing of micronutrients has not been established for clinical practice either for human studies. McAuliffe *et al*[1] mention that some groups may require doses higher than the Recommended Dietary Allowance (RDA) to meet the metabolic demands. Indeed, autoimmune diseases have been linked to vitamin D resistance, where higher amounts of that vitamin are required to exert its immunoregulatory effect.[8] Again, the profiling of metabolic products of micronutrients will provide a personalised overview of nutrient needs.

Now that we are facing the COVID-19 pandemic, actions must be taken so that practitioners are trained for the evaluation of the nutritional status using current methodologies but also promote measures for the validation of metabolomics nutritional biomarkers.

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