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The contribution of food bioactives and nutrition to the management of COVID-19

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ABSTRACT

Poor nutrition predisposes to infection, and various food compounds, such as micronutrients, are key elements of immune competence. A large number of scientific publications have suggested a role of phytochemicals, food bioactives and nutrition in combating the current coronavirus pandemic. Various dietary components and specific food supplements have been proposed to be helpful in the prevention or therapy of COVID-19. While findings in preclinical models suggest that food bioactives and micronutrients may potentially augment viral defense, evidence supporting antiviral and immunomodulatory efficacy of these compounds in the prevention or management of COVID-19 is non-existent. Large-scale epidemiological and well-designed clinical studies investigating dosage and combinations of food compounds in different age groups and populations are needed before any recommendations can be made. Both malnutrition and overnutrition can adversely affect the immune system. Malnutrition at population level appears to be associated with elevated rates of fatal outcomes of COVID-19. Obesity and non-communicable diseases have been found to be a prognostic risk factor associated with worse COVID-19 outcomes. A focus on obesity and nutrition-related chronic diseases should be a key element of public health. This approach would be more effective than the far less promising search for food bioactives with potential immune-supportive efficacy.

1. Introduction

At the beginning of the third year of the current coronavirus pandemic, it may be of value to assess the contribution of food and nutrition to the management of the coronavirus disease 2019 (COVID-19). Over 6 500 publications were found in a Pubmed literature search, performed on December 22, 2021, using the keyword combination "Food and COVID-19". Many of these papers, which were largely reviews of the available literature, suggest potential effects of micronutrients, such as vitamins and minerals, as well as phytochemicals and food bioactives, including polyphenols and carotenoids, in augmenting immune function and defending against COVID-19 [1-3]. Due to their immunomodulatory and antiviral properties, a wide range of functional food plants, such as garlic, ginger, pomegranate, elderberry, black pepper and turmeric, have been claimed to be capable of enhancing the immune system in general and curing respiratory tract infections in particular ("food as medicine") [4]. Furthermore, countless newspaper articles, website reports and social media stories convey the message that dietary supplementation of certain nutrients, "immunostimulants", antioxidant compounds and specific food bioactives is able to prevent the spread of the novel coronavirus and ameliorate the course of COVID-19. The present perspective argues that the available evidence in support of the utility of specific food bioactive and micronutrient supplementation in the current pandemic is insufficient and that food science should instead address the issues of malnutrition and especially overnutrition-related non-communicable diseases in contributing to the management of the pandemic.

2. Nutrients and food bioactives

COVID-19 is a multifaceted and multiple organ dysfunction

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syndrome, which shows pathological effects in the immune, cardiovascular, urinary, nervous, hepatic and gastrointestinal systems, in addition to those in the respiratory tract [5]. In individuals with a severe course of COVID-19, high levels of pro-inflammatory cytokines activated by the coronavirus may predict a fatal outcome [6]. In addition to the inflammatory process, oxidative stress may have an important influence on the severity of the disease [7]. This has led to the suggestion that a variety of food-derived antioxidants could be helpful in the management of COVID-19 through their oxidative stress reducing properties [2]. Antiviral efficacy of various food bioactives, such as carotenoids and polyphenols, has been suggested. For example, polyphenols have been found to be capable of influencing the suppression of pro-inflammatory gene expression and the synthesis of pro-inflammatory cytokines [8]. However, hypotheses regarding antiviral benefits of polyphenols [9] and carotenoids [10] are based on preclinical investigations in cell cultures or animal models. Controlled trials of such compounds in humans have not been conducted, and beneficial effects of food bioactives on viral infections in humans therefore remain uncertain. Probiotics have been shown to influence host immunological networks and to activate a wide range of immune mechanisms [11,12]. In particular, a modest reduction in the incidence and duration of viral infections of the respiratory tract has been reported [13-15]. While microbial dysbiosis has been found in some patients with COVID-19 [16], the efficacy of probiotics in the prevention or treatment of COVID-19 is unknown [17,18].

Various minerals, such as selenium, zinc, iron and copper, and several vitamins play important roles in physiological immune functions, and a healthy immune system is critically dependent on the homeostasis of these micronutrients [19]. Deficiencies in micronutrients have been shown to impair immunity to disease, while their supplementation has been reported to improve immunity to viral infections [20]. For example, an impairment of immune responses and an elevated risk of systemic infections seem to be associated with vitamin D deficiency [21]. Supplementation of vitamin D may prevent respiratory infections through a decreased production of pro-inflammatory cytokines and a reduced risk of cytokine storm causing pneumonia [22]. Numerous factors may affect the efficacy of micronutrients in infections. Such factors include the type of pathogen, the dose and duration of micronutrient supplementation as well as the genetics, age, lifestyle, nutritional and immunological status of the individuals receiving micronutrients [1]. Immunosenescence appears to be a particularly important factor in the effects of nutrition on immune functions [23]. Extended micronutrient supplementation at high doses may have unwanted side effects and may even aggravate infectious diseases [24-26]. Investigations of individual food agents capable of promoting optimal immune functions rely on the conception of precisely targeted “magic bullets” [27] and accord with the traditional methodology of clinical pharmacology. However, this research strategy fails to account for the physiological processes requiring the intake of numerous nutrients in balance. This may explain the limited success of the supplementation of single nutrients.

The arguments supporting the administration of micronutrients and food bioactives stem mainly from cell culture or animal studies [9,10,28,29]. Animal experiments usually apply a reductionist approach, i.e., the behavior and interactions of complex systems are investigated and explained in terms of their individual parts and mechanisms. A complex real life system is explained in terms of its constituent units, which can be more easily analyzed and comprehended. For example, in the case of food bioactives and micronutrients in infections, the impact of these compounds is investigated on single biochemical pathways and physiological outcomes rather than on the entire organism. While the reductionist approach is successful in explaining various mechanistic details of biological processes, it is unable to account for the complexity and dynamics of biochemical interactions in different body systems. In contrast, the approach of systems biology attempts to investigate the network of interactions between different biological systems and to describe complex outcomes, which are difficult to predict on the basis of individual mechanisms. Food bioactives can interact with and influence numerous organismic components and may have additive, synergistic or antagonistic effects. Thus, while the effects of food bioactives and their compounds may demonstrate positive effects in animals on various physiological mechanisms involved in immune functions, the net effect on immune responses in humans may be less pronounced than expected. It therefore seems apparent that different research strategies may explain different effect sizes for micronutrients and food biactives observed in animal and human research. Furthermore, several issues related to the choice of clinical outcome markers, dose-response relationships and potential adverse events require further investigation in humans.

3. Malnutrition

Malnutrition and nutritional deficits have been shown in clinical and epidemiological studies to impair immune responses and increase the risk of infection [30,31]. Malnutrition at population level appears to be associated with elevated rates of fatal outcomes of COVID-19. In several countries, particularly low-income countries in the Sahel strip and other regions of sub-Saharan Africa, malnutrition may have increased the rates of fatal COVID-19, as suggested by the association between a high burden of malnutrition and an increase in mortality from COVID-19 [32]. In these countries, preventive public health strategies addressing COVID-19 should incorporate food security and the production, distribution and consumption of healthy diets in order to improve the population-wide nutritional status and reduce COVID-19-related fatality rates. A marked increase in case fatality ratios for COVID-19 was also found in countries with very high rates of years lived with disability from iron deficiency [32]. Insufficient dietary intake of iron and in particular animal protein is a common cause of iron deficiency [33]. While the relationship between iron deficiency-induced anemia [34] and an increase in susceptibility to infectious diseases remains a matter of debate [35], sufficient iron supply should be included in food security considerations. Furthermore, vitamin A deficiency may add to the impact of undernutrition on COVID-19 fatality [32], particularly in sub-Saharan Africa, with its high prevalence of vitamin A deficiency [36]. Of particular concern is the possible exacerbation of COVID-19 effects in malnourished children in low-income and middle-income countries. In addition, more children are becoming malnourished due to interruptions in nutrition and deteriorating diet quality during the pandemic [37], with the global prevalence of child wasting possibly rising by 14% [38]. Thus, worldwide access to safe, nutritious and affordable diets needs to be safeguarded during the COVID-19 pandemic.

The impact of malnutrition on COVID-19 outcomes has also been investigated in high-income countries. Several studies have shown that long-term effects of malnutrition appear to predispose patients to a more severe course of COVID-19. In the United States, COVID-19 patients who were malnourished or at risk of malnutrition were found to have an increased risk of suffering more severe forms of the disease [39]. A close association between a malnutrition score and severity of COVID-19 and the outcome of hospitalization was reported in a study from Italy [40]. A meta-analysis of available studies found that the likelihood of mortality among malnourished patients with COVID-19 was 10 times higher than in those who were well-nourished [41]. Mitigating strategies are therefore needed to prevent and manage malnutrition and its outcomes. Furthermore, the well-known deleterious effects of disease-related malnutrition [42] can be contained by prompt nutritional supplementation [43,44].

4. Obesity and non-communicable diseases

As well as malnutrition, overnutrition-related non-communicable diseases, such as obesity, type 2 diabetes and metabolic syndrome, can negatively affect immune functions. Non-communicable diseases, such as hypertension, ischemic heart disease, type 2 diabetes, chronic obstructive pulmonary disease and cancer, have been linked to various infectious diseases, post-infection complications and death from infections [45,46]. Obesity rates have risen sharply, not only in high-income countries but also in low- and middle-income countries [47]. The globally high prevalence of obesity and non-communicable diseases also appears to contribute significantly to the impact of COVID-19 [48]. An association between severity of COVID-19 and non-communicable diseases has been reported in various countries [49]. For example, diabetes is known to carry an elevated risk for infections. In a nationwide study from Sweden, type 2 diabetes patients infected with SARS-CoV-2 were twice as likely to require hospitalization, to be admitted to intensive care and to suffer a fatal outcome for COVID-19 [50].

The body-mass index appears to be associated with the severity of COVID-19, with patients suffering from severe COVID-19 and non-survivors typically having a body-mass index greater than 25 kg/m^2 [51]. Obesity has been shown to be a prognostic risk factor associated with worse COVID-19 outcomes [52], independently of age, sex or other comorbidities [53]. A chronic pro-inflammatory state, an excessive oxidative stress response and impaired innate and adaptive immune responses are linked to obesity and may underlie the strong association of obesity with a more severe course of COVID-19 [54-56]. Obesity and excessive visceral adiposity have been found to increase the risks for hospitalization, requirement of admission to an intensive care unit and of invasive mechanical ventilation as well as a fatal outcome among individuals with COVID-19 [57-60]. For example, the need for mechanical ventilation progressively increased with body-mass index, with almost 90% of patients with a body-mass index higher than 35 kg/m^2 requiring mechanical ventilation [57].

During the pandemic, obesity and non-communicable diseases may be addressed by dieting. In addition, regular moderate physical exercise has been shown to be associated with a decrease in the incidence of infection [61,62], particularly viral infections of the upper respiratory tract [63,64]. Preventive weight loss programs to reduce overweight and to encourage healthier food choices in order to avoid future weight gain may include large-scale television and social media advertising [65]. Weight reduction campaigns could follow a high-risk approach and focus on overweight and obese people, in view of their elevated risk for a severe disease course and fatal outcome of COVID-19. However, since disease risks are not categorical, but rather quantitative phenomena with a continuous distribution of the degree of risk, population-wide prevention measures may shift the risk distribution within large groups of people, thereby possibly decreasing the burden of disease more profoundly than merely targeting individuals at high risk [66].

5. Conclusion

Poor nutrition predisposes to infection, and various food compounds are key elements of immune competence. Therefore, a balanced diet containing sufficient amounts of nutrients as well as diverse micronutrients and food bioactives may aid immune support and help combat COVID-19. While findings in preclinical models suggest that food bioactives and micronutrients may potentially augment viral defense, the specific roles of these food agents in human viral infections remains unknown. Studies of cell cultures and animals can provide insights into the possible mode of action and potentially harmful effects of food agents, but they do not reflect the complexity of human physiology, and the translational relevance of their findings is therefore uncertain.

Evidence supporting antiviral and immunomodulatory efficacy of single nutrients, food bioactives or functional food plants in the prevention or management of COVID-19 is non-existent. Large-scale epidemiological and well-designed clinical studies investigating dosage and combinations of food compounds in different age groups and populations are needed before any recommendations can be made. Healthcare providers and patients should not therefore rely on food supplements in the prevention or management of COVID-19. Nobody would consider the use of vaccinations for COVID-19 if the evidence for their efficacy were as tenuous as that for food bioactives.

The findings of deleterious effects of obesity and metabolic disease in COVID-19 emphasize the need for effective action by individuals, the public and governments in order to increase awareness of obesity-related risks. Governments carry the responsibility to tackle obesogenic environments and unhealthy lifestyle factors. A continued and strengthened focus on the prevention and management of non-communicable diseases should be a key element of current public health, and the COVID-19 response should include the needs of those with nutrition-related chronic diseases. This approach would be more effective than the far less promising search for food bioactives with potential immune-supportive efficacy.

Declaration of interest

I declare that there is no conflict of interest.

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