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Nutritional fat modulation as a non-pharmacological approach to children infected with COVID-19, a challenge in food biochemistry

Hoda Atef Abdelsattar Ibrahim

Pediatric Clinical Nutrition Unit, Pediatric department, Children Hospital Cairo University, Faculty of Medicine, Cairo University.

Abstract

WHO confirmed that COVID-19 disease is a pandemic event on March 11, 2020. The causative organism is a new virus called SARS-CoV-2. The review aims to explore the effect of nutrition-in particular the fat component - on the COVID-19 course in pediatrics. In this review, I will explain the relationship between the dietary fat component and its role as a macronutrient in the modulation of the disease severity or the prevention. The modification could be in the type or the amount of the dietary fat. To illustrate, it is advisable to avoid the saturated and trans-fatty acids due to their links to obesity with subsequent raised risks for COVID -19. In addition, the amount of dietary fat can be ameliorated to yield better disease outcomes. To illustrate, the ketogenic diet (high fat diet) provides the betahydroxybutrate which has favorable effects on the immunity suppressing and delaying the cytokine storms.

Keywords: COVID -19; dietary fat; pediatrics; cytokine storms.

1. Introduction

Coronavirus spread in a rapid manner, leading to an epidemic in China, followed by a rapidly increasing number of cases through the world. In February 2020, the World Health Organization (WHO) identified the disease as COVID-19, that is standing for coronavirus disease 2019 .The virus that causes COVID-19 is identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV. The WHO has declared this disease as a pandemic on March, 2020. Children at all ages can acquire COVID-19 (1-3). Children appear to get the virus less commonly than adults (4-13).In surveillance from various countries, children account for up to 13 percent of the confirmed cases.(14-20)

Multisystem inflammatory syndrome in children is a rare and serious condition occurs in association with COVID-19. The pathophysiology of multisystem inflammatory syndrome is supposed to be immune dysregulations .It has been supposed that this syndrome results from an abnormal immune response to the COVID -19.Cytokine storm is a term used to describe different pathologies including macrophage activated syndrome , cytokine release syndrome , sepsis and acute respiratory distress syndrome . Severe COVID -19 causes a pro-inflammatory cascade leading to vascular leakage and lung damage.(21)

Obesity as a risk factor for COVID -19

Overweight and obesity exists when the weight to length / height is higher than the mean by two and three standard deviations (SD) respectively of the WHO Child Standards for growth or BMI (Body Mass Index) is higher than 85th and 97 th centile for age respectively .(22-24)

Obesity is one of the preexisting diseases which is associated with death in pediatric patients with COVID -19 . Several studies around the world determined obesity and severe obesity as risk factors for mechanical ventilation and hospitalization .(25)

Impaired metabolic health and obesity are addressed risk factors for type 2 diabetes mellitus, cardiovascular disease, cancer and metabolic associated fatty liver disease (MAFLD). With the pandemic spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), obesity also emerged as an essential determinant of COVID-19.(26)

Currently, during the Corona epidemic in Canada, obesity was observed to be the third most prevalent

*Corresponding author e-mail: hodaibrahim424@gmail.com; (H. Atef)
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demographic factor for critical children admitted to the intensive care unit, behind only those with immunosuppression, serious associated diseases, and cancer (27). In New York, obesity was observed to be the most prevalent comorbidity among fifty severe cases of COVID-19 affecting both the children and adolescents. (28)

Obesity is an essential prognostic factor related to the intensive care mortality during COVID-19 pandemic (29). A remarkable transfer of COVID-19 disease severity to children has been identified through obesity. Obesity has effects on many vulnerable functions, causing an increased risks towards Corona potential .

Obesity can restrict the ventilation through disrupting movements of the diaphragm, decreasing the immune defense against viral infections (30), and exacerbating the oxidative stresses and the glucose intolerance (31).Notably, children with obesity experience a severe course with Corona as obesity can cause an alteration in the hemostatic balance through defective fibrinolysis and increased coagulation, that leads to a pro-thrombotic condition.(30), (32). Furthermore , the combination of the metabolic-associated fatty liver disease and obesity yields a six-fold amplified risk for severe prognosis of COVID-19. (33).

Importantly, it was addressed that considerable levels of transcripts for ACE2 are present in the adipose tissue. ACE2 is an enzyme linked to the surface membranes of the pneumocytes, that is a target for COVID-19, to enter and subsequently infect the cell ,so whether fatty tissue may be a reservoir for COVID-19 , and a site to enhance subsequent cytokines series activated via the infection should be investigated.(34)

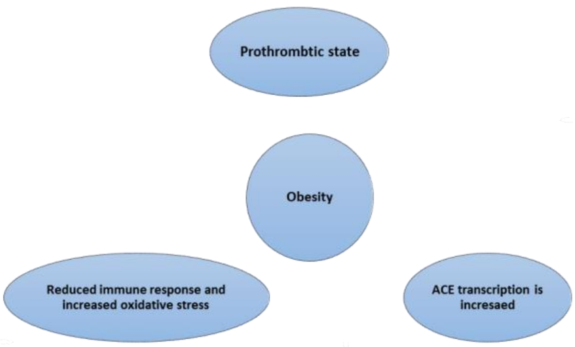

Figure 1 : How is obesity a risk for COVID -19 ?

Dietary policy to avoid obesity :

1.Low trans fatty acids and saturated fats to avoid obesity:

Dietary fats and their relation to pediatric obesity have been controversial issues for several years. Clinical studies yield that trans fatty acids have the ability to increase insulin resistance. The differences in the response of inflammatory signals and of the insulin resistance to different fatty acids show that not all fatty acids are the same. In a study done by Scholz , et al , It was found that , higher intakes of industrial trans fatty acids were positively linked to overweight and obesity in 4 to 5-year-old Spanish children. In addition, consuming processed foods rich in saturated fats, including fried foods and fast food, has been consistently associated with an increased risk of obesity.(35)

Glycemic index (GI) – lipid profile link and obesity

Associations have also been found between GI and both undesirable lipid profile and the consequent raised inflammatory status. It was found that fasting triacylglycerol levels were positively related to the glycemic index . Serum HDL levels have been established to be negatively related to the glycemic index.. Plasma levels of C-reactive proteins, high and sensitive markers of systemic inflammation, were found to be strongly associated with both the glycemic index and blood glucose with a stronger relationship in overweight individuals than in normal-weight ones . Therefore , hyperglycemia and the subsequent high glycemic state should be promptly prevented to improve the prognosis of these patients. In addition , It was demonstrated that a carbohydrate-restricted diet, utilized shortly, extremely decreased weight in large proportions of severely obese children and adolescences. Subsequently , the decreased weight could be an approach to avoid potential risks for severe COVID-19 .(36)

Importantly, a dietary approach that lowers serum glucose concentrations should be considered as a first choice, to avoid or diminish Sars-Cov-2 infection risks and complications (37). Furthermore , low glycemic index diets provide more stable profiles, lowering the postprandial hyperglycaemia and hyperinsulinaemia, and decreasing the late postprandial rebound in free fatty acids in the blood , all factors that exaggerate the metabolic syndromes .

Modification of the amount of fat

Ketogenic Diet

Ketogenic diet is a high-fat, low-carbohydrate diet with adequate protein which is a non-pharmacologic management for resistant epilepsy.

It is a diet that mimicked the metabolic effects of fasting by inducing ketosis (a state in the body where ketone bodies replace glucose as the major source of energy).(38)

Reduction of (Carbon dioxide) CO2 load

The ketogenic diet can significantly reduce stores of carbon dioxide particles in the body , that may be beneficial for children with increased carbon dioxide arterial partial pressure due to respiratory failure or insufficiency.

Published studies of respiratory failure that is precipitated by feeding with high

carbohydrate have drawn the attention to the fat and carbohydrate content of the child's diet. In children with acute or chronic retention of carbon dioxide (Hypercapnia),an aim of the dietary management is to diminish carbon dioxide production. High carbon dioxide production precipitates acute respiratory failure in children with chronic pulmonary diseases and may complicate weaning in ventilator dependent children. Because the complete combustion of dietary fats yields less carbon dioxide than combustion of either protein or carbohydrate, a high fat diet is preferable for children with pulmonary diseases .(39)

Low CHO (carbohydrates)

An evidence was provided that high levels of blood glucose importantly contributed in the viral amplification and replication. Excitingly, COVID-19 infection influences the mitochondrial ROS (reactive oxygen species) production, that enhances the maintenance of hypoxia-inducible factor-1α (HIF-1α) that sequentially changes the metabolic features of monocytes/ macrophages into glycolytic mainly, resulting in an enhanced replication rate of SARS-CoV-2 (40).

Soliman et al. supposed that the intermittent fasting can be a potential prophylactic strategy to block COVID-19 infection. This can be achieved through changes in the metabolic pathway from a carbohydrate-reliant pathway to a fat-reliant ketogenic pathway aiming to alter or change viral factor-kB in macrophages, microglia and dendritic cells and subsequently decreases the nervous inflammation . (45)

Endogenous OHB (Beta-hydroxybutyrate)

Ketogenic diet is supposed to affect the innate and adaptive immunity , that synergistically provide children the protection against the pathogens' assaults. Firstly, cells of the innate immunity are triggered by the viral antigens via activations of the pattern recognition receptorNLRP3(nucleotide binding domain (NOD)-like receptor protein 3), to suppress the replication of virus. In keeping with this, the NLRP3/inflammasome can be considered as an essential innate immunity sensor that mediate virus-triggered inflammation by means of triggering replication (41).Such this metabolic shift can cause a raised resistance to the mitochondrial stress, an improved autophagy ,DNA repair, an improvement in antioxidant defenses, and a decreased insulin secretion (42). In consideration of these reasons ,ketogenic diet can be considered as a dietary therapy for successful immunological responses against COVID-19 infection (43).

Importantly, a recent study suggested the role of the oral glucose reduction in decreasing macrophage M1 polarity early in the inflammatory steps (44). Indeed, phenotype M1, whose activation has a role in the cytokine storm syndromes, depends strongly on the glycolysis aerobically, that is reported to be reduced by a remarkable decline in the glucose uptake, as it ensues through the ketogenic diet . Moreover, the ketogenic diet can maintain the M2 macrophages anti-inflammatory metabolism , that excessively express the OXPHOS (The oxidative phosphorylation system) enzymes via continuous existence of the free fatty acids (45). M1-like macrophage role is critical at the earlier stages of the infection to elicit the initial inflammatory response stimulating immune cells in autocrine and paracrine fashions, while M2-like macrophages are mandatory for the resolution of inflammatory responses and healing damaged tissues.(46)

Reducing Oxidative stress

By simultaneously declining ROS(reactive oxygen species) production and raising the level of endogenous antioxidant capacity, ketosis can protect tissues from possible oxidative stress.

Ketogenic diet can minimize blood glucose spikes, lowering oxidative stresses in mice, and inflammatory markers in humans. Ketogenic diet, through raising the levels of hydroxybutyrate, is capable of hydroxycarboxylic acid receptor 2 activation, that is a G protein-coupled receptor which suppresses nuclear of Interleukine-18 (IL-18) secretion and Interleukine-1β (IL-1β) . The pattern recognition receptorNLRP3(nucleotide binding domain (NOD)-like receptor protein 3)is a nucleotide oligomerization domain (Nod)-like receptor (NLR) which identifies the damage-associated molecular patterns (DAMPs), e.g. cholesterol crystals, toxins, excess of glucose, bacterial and viral molecules. To demonstrate, RNA viruses have the ability to activate NLRP3 by means of the antiviral mitochondrial signaling protein (MAVS) on the mitochondrial outer surface membrane.(47)

Activated NLRP3 enhances the inflammasome complex formation that interact with the adaptor protein ASC (apoptosis-associated speck-like protein containing C-terminal caspase recruitment domain

[CARD]),that, in turn, change the zymogen procaspase-1 activation into caspase-1. As a final step, the inflammatory caspase-1 changes the inactive pro-Interleukine-1β (pro-IL-1β) and pro-Interleukine-18 (pro-IL-18) into their active proinflammatory cytokines (48)

The viral induced NLRP3/inflammasome activation has been observed for, encephalomyocarditis virus (EMCV), influenza A virus(IAV), SARS-CoV, hepatitis C virus (HCV) (49) that assembles into homo-oligomers and form hydrophilic pores through the cytosolic organelle membranes, subsequently, increasing Ca2+, Na+ and K+ flux. Raised levels of intracellular calcium and declined levels of intracellular potassium are considered to be important triggering factors for NLRP3/inflammasome activation .Subsequently, excessive secretions of proinflammatory cytokines can be produced. It is established that OHB suppresses NLRP3/inflammasome activation. The desirable outcomes of the ketogenic diet on inflammatory cytokines in humans, and in animal are established. OHB has the ability to mediate on a crucial signaling pathway which is precise to the NLRP3/inflammasome, as a result of different pro-inflammatory stimuli activations. More specifically, OHB inhibits NLRP3/inflammasome activation by diminishing K+ efflux from macrophages and the suppression of the inflammasome assembly. Thus , OHB-dependent suppression of IL-1β and IL-18 secretion can occur.
In the view of the active inflammasome function in stimulating the systemic inflammatory cascade in patients with COVID-19 , trials which are centered on raising plasma OHB, such as ketogenic diets , should be respected to prevent or delay the progress and the deterioration of cytokine storm syndromes. (50)

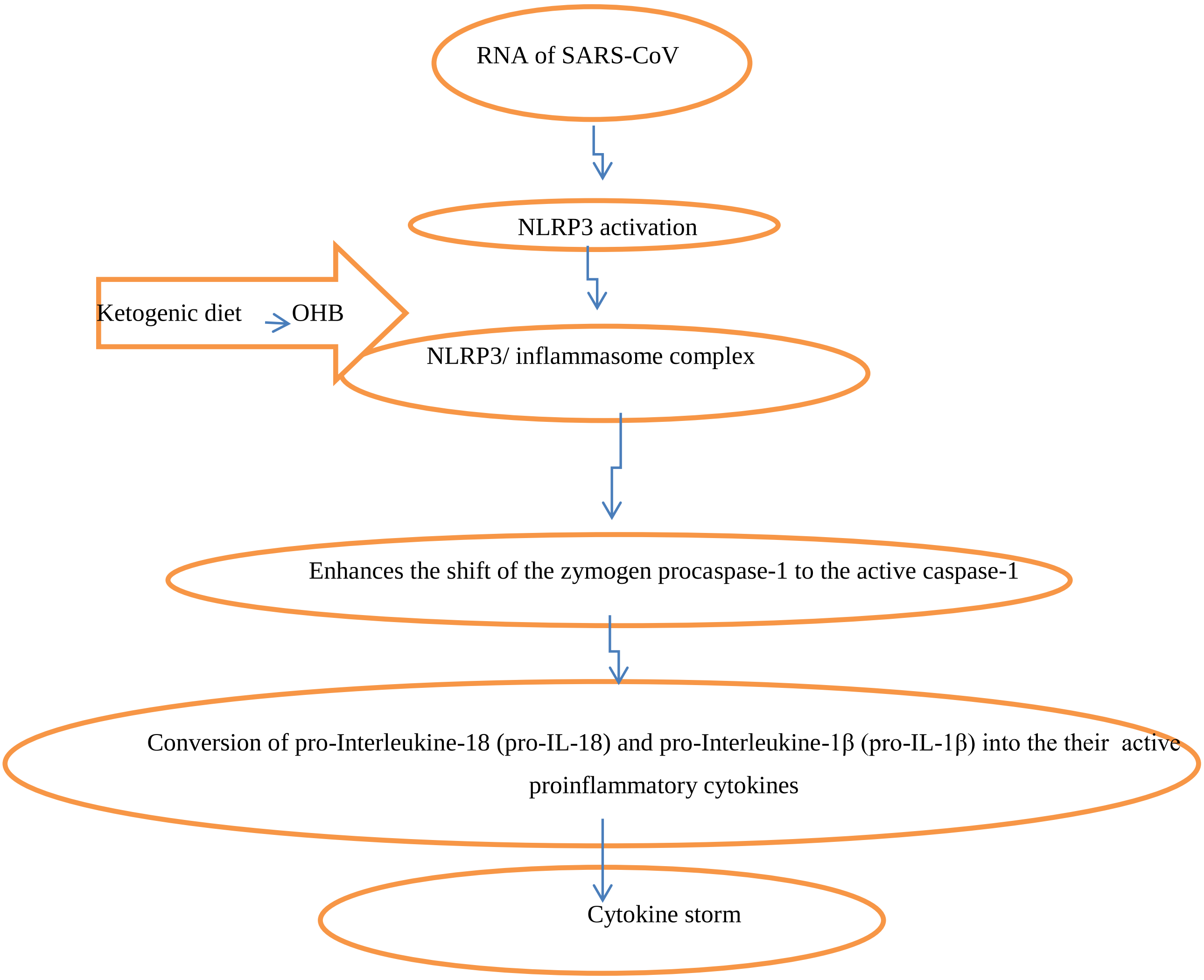

Figure 2 : How can ketogenic diet prevent cytokine storm?

With a higher fat content may decrease requirements for artificial ventilations and thus diminish the duration of mechanical ventilation.This can markedly decrease mortality and morbidity linked to mechanical ventilations.

It was found that better feeding practices in terms of high fat component affected the outcome of critical children that is represented in a remarkable reduction in the arterial Co_2 tension, tidal volume, minute volume, peak inspiratory pressure that reduces the duration of artificial ventilation and facilitates weaning. Thus, leaving children with respiratory failure as a result of any pulmonary disease during the admission in the intensive care unit and who are planed for artificial ventilations to the already present dietary practices with the ordinary feeds will further hinders the parameters of the ventilation in these children and will delay weaning from it. Feeding these children with low carbohydrate high fat regimen will prevent further impairment of these parameters and consequently will influence weaning and favorably affect outcomes of the hospital stay in the intensive care unit .Considerable efforts should be taken regards this feeding to be applicable and properly nourish these children and prevent any expected deterioration in their status.(54)

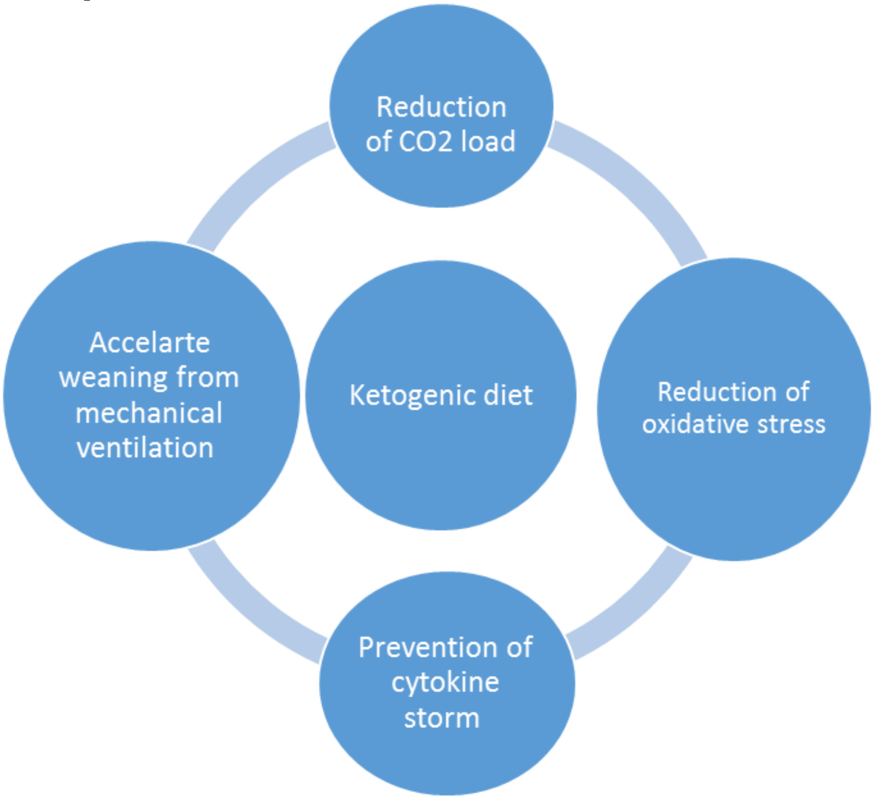

Figure 4 : The role of ketogenic diet in the COVID-19 course.

Supplement :

omega 3 fatty acids

In 146 patients with adult respiratory distress syndrome (ARDS) supplied with an enteral nutrition rich in eicosapentaenoic acid, γ-linolenic, a remarkable improvement in PaO2/FiO2 ratio and a reduction in pulmonary inflammatory response, days of mechanical ventilation , frequency of new organ failures, and length of hospital stay in the intensive care unit were observed. In 100 patients who were having acute pulmonary injury receiving a similar enteral nutrition , pulmonary compliance and oxygenation were better, and there were less needs for mechanical ventilation . Omega 3 fatty acids parentally have been reported to improve the glucose metabolism and reduce inflammatory markers after major surgery .(55)

Fat soluble vitamins

Vitamin D

Receptors for vitamin D are expressed in innate immune cells (e.g., macrophages, monocytes and dendritic cells).They enhance the differentiation of monocytes to macrophages. In addition , they stimulate the proliferation of immune cells and the cytokines production . Moreover , it provides protection against infections .(56)

It was concluded that vitamin D levels might be important in the prediction of severe forms of multisystem inflammatory disease related to COVID-19 . In addition, correction of any abnormal levels found can influences its evolution. 25-hydroxyvitamin D3 [25(OH)D3] supplementations raising serum [25(OH)D] concentrations effectively have a favorable potential result in decreasing the severity of multisystem inflammatory disease related to COVID-19 in pediatrics.(57)

In a study done by (Yılmaz, et al ,2020). Vitamin D levels were evaluated for their link with the clinical pictures in COVID-19 children . The findings suggested that vitamin D levels may be linked with the treatment of the COVID-19 disease by modulating the immunological pathways to the virus in the pediatrics.(58)

Vitamin A

It maintains the integrity of the function and structure of the mucosal cells in the innate barriers (e.g., skin, respiratory tract, etc.). Furthermore, it is essential for functioning of the innate immune cells (e.g., NK
cells, macrophages and neutrophils)

Vitamin E

It is an essential fat-soluble antioxidant. In addition ,it supplies protection to cell membranes from free radicals damage .Moreover, it influences IL-2 production and natural killer cell cytotoxic activity .(59), (60)

Table 1: Modification of dietary fat

Modification of the dietary fat
In the type mainly Low saturated fats low trans fats To avoid obesity and its risks for COVID
In the amount Ketogenic diet Low CHO Decrease Co2 load Decrease the glycolytic metabolism reducing COVID replication Increasing OHB Inhibits NLRP3/inflammatose activation T cell expansion
Supplement Omega Improve pulmonary compliance Decrease inflammatory markers Vitamin D modulate immune mechanism

Conclusion:

Modification of the dietary fat can protect or decrease the severity of COVID -19 in pediatrics. obesity has comorbid risk factors, so a diet that could decrease the possibility of obesity can reduce the subsequent susceptibility to severe Covid-19 course. In addition, raising the amount of the dietary fat in relation to other macronutrients - as it occurs via the ketogenic diet – can yield anti-inflammatory signals as OHB that reduces the severity of cytokine storms. Furthermore, fat soluble vitamins and supplement such as omega have great roles in raising the immunity against COVID-19.

Recommendations

Attention should be paid to the healthy food pyramid. First , the macronutrients could be modified . To illustrate , simple carbohydrates should be avoided due its link with the undesirable lipid profile with subsequent raised inflammatory status. In addition, the caloric percentage of fat could be increased at the expense of carbohydrates in cases of chronic lung affection to decrease carbon dioxide load . Second , the micronutrients could be also modified . For example, foods rich in vitamin D and vitamin A such as oily fish and egg yolk should be considered. Egg yolk is rich in omega as well . Besides, foods rich in vitamin E such as green leafy vegetables and nuts are preferred. The main aim of this modification of micronutrients is to increase the antioxidants level boosting the immunity.

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The author reports that no conflicts of interest in this work are present.

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