

PREGLED LITERATURE – REVIEW ARTICLE

Child Obesity Epidemic During the Corona Virus Pandemic – What Does it Have to do With Vitamin D?

Epidemija gojaznosti dece tokom pandemije korona virusa – kakve to veze ima sa vitaminom D?

Aleksandar Marković¹, Maja Jović¹, Milica Ćosić², Tatjana Jevtović Stoimenov³

1 Naučnoistraživački centar za biomedicinu, Medicinski fakultet Univerziteta u Nišu, Srbija

2 Infektivna klinika UKC Niš, Medicinski fakultet Univerziteta u Nišu, Srbija

3 Katedra za Biohemiju, Medicinski fakultet Univerziteta u Nišu, Srbija

Summary This review paper summarizes current knowledge and understanding of the associations between corona virus epidemics and obesity with the role of vitamin D. As the whole world is in the midst of the coronavirus epidemics, other conditions/diseases are currently not in focus. It has been observed that the tendency towards obesity is increasing, and is perhaps significantly higher than expected, where one can define it as an epidemics as well. Vitamin D has been shown to play multiple roles in both epidemics. The most significant connection could be seen in the role of vitamin D as an immunomodulator, and suppressor of the oxidative stress and cytokine production. These correlations, and many others, have been discussed in this paper, since all of them could be related to both obesity and covid-19 infection. There is well known correlation between obesity and vitamin D deficiency, since in certain cases the treatment of obesity includes the supplementation with this vitamin. Through this treatment regiment one might also increase the prognosis of covid infection, since both vitamin D deficiency and obesity are known to be associated with poor covid infection prognosis.

Key words: obesity, COVID19, vitamin D, children, pandemic

Sadržaj Ovaj pregledni rad sumira trenutno znanje i razumevanje povezanosti između epidemija virusa korona i gojaznosti sa ulogom vitamina D. Pošto je ceo svet usred epidemije koronavirusa, druga stanja/bolesti trenutno nisu u fokusu. Uočeno je, da je tendencija gojaznosti u porastu, a možda i znatno veća od očekivane, pa se i definiše kao epidemija. Pokazalo se da vitamin D igra višestruku ulogu u obe epidemije. Najznačajnija veza se može videti u ulozi vitamina D kao imunomodulatora i supresora oksidativnog stresa i proizvodnje citokina. Ove korelacije, kao i mnoge druge, razmatrane su u ovom radu, jer sve one mogu biti povezane i sa gojaznošću i sa infekcijom covid-19. Postoji poznata korelacija između gojaznost i nedostatka vitamina D, pa u određenim slučajevima lečenje gojaznosti uključuje i suplementaciju ovim vitaminom. Može se poboljšati i prognoza kovid infekcije, pošto je poznato da su i nedostatak vitamina D i gojaznost povezani sa lošom prognozom infekcije covid-19.

Ključne reči: gojaznost, COVID19, vitamin D, deca, pandemija

Obesity

Obesity is defined as an excess fat sufficient to increase the risk of morbidity, altered physical, mental or social well-being and / or mortality. The incidence of childhood obesity, In the latest decades, has increased considerably, which significantly impacts children's health (1). Recent estimates, from the data arriving from 2016, suggest that around 40 million children under the age of 5- and children over the age of 5 and under the age of 19, there are more than 330 million of them whit overweight or obese (2).

According to the World Health Organization (WHO) - every third child in the European region is overweight or obese. and more than 60 percent of overweight children before puberty will be obese in early adulthood (3).

These tendencies have led member states of the WHO to support the goal that by 2025 obesity in children all age will not increase (4). It has been recognized that the main initiators of the current obesity epidemic are associated with changes in food intake and reduced physical activity (5). These factors are associated with the availability of generally economical, energy-rich and over-processed food and sugar-sweetened drinks, as well as with the fact that people live a sedentary lifestyle, with very little physical activity among children. In the pediatric age group, percentile gender-specific BMI-for age curves are used to define overweight and obesity. The BMI has a high correlation with adiposity, as well as with excess weight at the population level.

It is important to note that the calculated BMI isn't always correct because it doesn't account for total body fat or distinguish between lean/muscle and fat mass.

However, at the population level, BMI tends to follow adiposity rather than muscularity changes. A simple body inspection can tell the difference between people who have a lot of muscle mass and a high BMI and those who have a lot of adipose tissue. (6,7).

Values of BMI above 85, and less than 95 percentiles in children and adolescents, are considered overweight, while those with more than 95 percentiles per BMI are classified as obese. Children of all ages with BMI greater than the 99th percentile are classified as severely obese. The International Obesity Working Group has created an international standard growth chart that may be used to compare obesity prevalence throughout the world. The usage of country-specific growth charts, on the other hand, is still common.

In the United States, for example, the gender-specific CDC Growth Charts have been used to assess BMI for children aged 2 to 20 years since May 2000. Being overweight in childhood and adolescence continues to be one of the most serious health issues; nevertheless, it should be highlighted that treating obesity is quite tough. Combating the childhood obesity pandemic will need a collaborative effort across several sectors, including the economy, education, nutritious food in metropolitan areas, and universal health care, but most importantly, primary prevention is essential to reduce the incidence of obesity in children (6,7).

Waist circumference measurement, in addition to BMI, is another easy method for detecting obesity. Waist circumference has been found to link more strongly than BMI with various problems in children, including dyslipidemia, insulin resistance, and nonalcoholic fatty liver disease. (7).

Obesity in children has the potential to harm practically every organ system, including the respiratory system, since it increases oxygen intake while also increasing carbon dioxide generation. Obesity raises the risk of numerous chronic illnesses, including dyslipidemia, hypertension, diabetes, cardiovascular disease, asthma, sleep apnea, and osteoarthritis, since it is a proinflammatory condition. (6). Childhood obesity has been shown to alter the immune system by promoting a proinflammatory condition. It is observed that in young people with obesity, there is an increase in cytotoxic and effector T cells (Th1 and Th7) and M1- macrophages, together with decreased levels of regulatory T cells and M2 macrophages (8). Molecules involved in this immune system disfunction due to obesity involve adipocytokines (leptin) and cytokines (IL-6, IL-12, TNF- α , IL-1 β , MCP-1 and nitric oxide) which might be the reason for the worse clinical outcome in children with COVID-19 infection (9). Also, one should not forget that

childhood and adolescent obesity could be linked to adulthood mortality and premature death (5).

COVID19 infection

The infection caused by the SARS-CoV-2 is spread worldwide since the end of 2019, causing a pandemic (10). According to the data given by the American Academy of Pediatrics, the children are affected in around 14.2% of all confirmed Covid-19 cases. Additionally, on 100 patients every 1-4 is a child, and the death toll from this infection in children is 0.00–0.24% (11). The virus causing the respiratory infection is not a new class of virus, but rather an old one (*coronaviridae*) which were previously associated with mild upper respiratory tract infections. However, the current virus is provoking much serious infection which is up to now known to be due to factors unique to the virus, host and environmental interactions (12).

COVID19 mostly affects the respiratory system, and clinical outcomes ranges from asymptomatic to lethal outcomes (13). A number of factors, including age, diabetes, hypertension, and ethnicity, are held responsible for the increased risk of COVID19. Also, vitamin D (vit. D) deficiency has emerged as another potential risk factor for COVID19. It was also noted that obesity in children was shown to correlate with a worse prognosis of COVID-19 and that obesity was the most significant factor associated with the need for mechanical ventilation in children older than 2 years, in line with what has already been described in obese adults affected by SARS-CoV-2 infection (14). A recent meta-analysis and systematic review described that children with earlier comorbidity were at higher risk of severe manifestations of COVID19 and mortality compared with healthy children. In addition to the factors involved in the exacerbation of severe COVID19 disease in obese patients, inflammation plays a key role; Visceral adiposity has been shown to enhance inflammatory cytokines, such as interleukin-6 and C-reactive protein, which correlate with enhanced severe manifestations of COVID19 (15). There is difference in how the child, compared to the adult, organism reacts to the COVID19 infection, and there have been some speculations regarding this difference. This difference may be due to the different antigen towards which the antibodies are formed, namely in children there is a more pronounced generation of IgG towards S-protein, while in adults the reaction is mainly towards S-spike protein, rather than towards S-protein. Also, it is suggested that the clearance of the virus in children is mediated through more pronounced innate immune system reaction, which predominantly involves macrophages (16).

During lung damage, a regular vitamin D intake leads to a decrease in RAS function, followed by an increase in the concentration of ACE2 receptors. Research shows that vitamin D deficiency can cause an increase in angiotensin II and/or a boost in RAS activity. It is responsible for the increased availability and expression of ACE2, as well as for increasing the levels of special sACE2 which has the

enzymatic activity, sACE2 receptors that bind S protein which further blocks the infection of the covid19 in cell (17).

Vitamin D

Vitamin D, a secosteroid hormone, is primarily synthesized in the skin from 7-dehydrocholesterol after exposure to ultraviolet (UV) radiation from sunlight and food consumption. The majority of research in the literature established a link between vitamin D status and oxidative stress and inflammatory indicators including C-reactive protein (CRP), interleukin-6, and others (IL-6). The response to the modulation of immune cells activity by vitamin D depends on the vitamin D receptors (VDRs) expressed by these cells. One of the recently proven functions of VDRs is the prevention of the T cells, dendritic cells and macrophages response to various stimuli (16).

As a hormone he has a role in immunomodulation in vitro and in vivo, its active form inhibits the differentiation of monocytes into dendritic cells, inhibits the activation of T cells and secretion of various interleukins IL-1, IL-2, IL-6, IL-12, tumor necrosis factor (TNF) alpha, TNF beta. Inhibits and interferon-gama as well as the expression of costimulatory molecules leading to an increase in the anti-inflammatory profile of CD4 + T cells. These cytokines play a major role in the both covid-19 and obesity (18).

There is evidence that status of vitamin D in children any age has been seriously investigated around the world, especially in Europe and in US. Data available for children of all ages show that hypovitaminosis D is widespread. Obesity, as a risk factor, also plays a role in vitamin D insufficiency, with multiple studies establishing a relationship between vitamin D deficiency and obesity. According to research, vitamin D shortage in overweight children is caused by volume dilution, decreased exposure to sunshine, and vitamin D buildup in adipose tissue, which limits bioavailability and may hasten some pathological processes. Hereditary factors appear to be responsible for 30 to 50% of the variation in adiposity (19).

Potential connections between obesity, COVID19 infection and vitaminD

The fact that the limited permeation between the genetic determinants of vitamin D status and the genetic determinants associated with obesity is surprising and may indicate two different stories. On the first, this could indicate a lack of studies investigating the impact of variations in non-VDR genes on obesity. While in the second case it might have a great biological importance, suggesting that variation in vitamin D receptors (VDR) is a more precise determinant of obesity phenotype than circulating 25(OH)-D concentrations. Since VDR protein is found in adipose tissue, it can be concluded that vitamin D has an effect on adipocytes. Thus, reported associations between obesity and VDR polymorphisms may be associated either with a direct effect of vitamin D on adipocyte differentiation and

metabolism, or with an indirect effect by modulating insulin secretion (20).

Recent research has found that macrophages, which imply alveolar macrophages are crucial for the development of the hyperinflammatory response in the lungs of COVID-19 patients, they also have an inducible expression of vitamin D 1 α -hydroxylase CYP27B1 that converts the inactive form of vitamin D to its active metabolite 1,25 (OH)₂ D that binds macrophage VDRs. Also, as mentioned previously macrophages are crucial for the virus elimination (16). This potentially could be one of the meeting points between the obesity and COVID-19 infection, with the function of vitamin D. Zhang et al. showed that vitamin D treatment increased the binding of the VDR to the DNA vitamin D response element in the mitogen-activated protein kinase phosphatase-1 (MKP-1) promoter. This caused the upregulation of MKP-1 expression, and, in turn inhibited the production of pro-inflammatory IL-6 and TNF- α in the monocytes and macrophages (21).

Studies on the chronic inflammatory lung disease such as cystic fibrosis showed that vitamin D, acting through its receptors, upregulates transcription of the anti-inflammatory Dual specificity protein phosphatase 1 (DUSP1) gene, which down-regulates the expression of inflammatory chemokine IL-8 produced by hyperinflammatory macrophages (22). This suggests a therapeutic potential of vitamin D for the treatment of inflammatory lung diseases which are associated with the production of IL-8. Also, a recent large-scale analysis of COVID19 patients suggests that vitamin D activates the innate, and suppresses the adaptive immune response, which, by lowering the cytokine expression level may down regulate the hyperinflammatory response responsible for the severity COVID19 infection and associated mortality. In line with these findings, the National Institute of Health, several clinical trials, which assessed the efficacy of vitamin D in the prevention and treatment of COVID19. A recent studies by Rastogi et al. show that a high dose of vitamin D supplementation, by oral administration, helped to achieve SARS-CoV-2 RNA negativity along with a significant decrease of the inflammatory markers (23,24). Moreover, Maghbooli et al. have shown that the correct levels of 25-hydroxyvitamin D reduce the risk of cytokine storm and serious response to COVID19 infection in patients (25).

In the study of Hernández et al., which involved 216 patients with COVID19 infection and 197 controls, vitamin D deficiency was significantly greater in the COVID19 group. A substantial inverse relationship was discovered between mean vitamin D levels and the frequency of COVID19 patients. (26). Merzon et al.'s study of 7807 patients found a strong correlation between vitamin D levels and the frequency of COVID19 cases. In addition, patients with COVID19 infection exhibited reduced vitamin D levels in a retrospective observational research with 186 positive cases and 2717 negative controls. (27). Others, on the other hand, claim that severe cases of COVID19 infection in particular groups cannot be explained by vitamin D insufficiency (28).

There was no relationship between the risk of COVID-19 and vitamin D levels in biobank studies conducted in the United Kingdom (29).

Vitamin D concentration is essential for development, growth and health. Vitamin D concentration is essential for development, growth and health. Obesity and COVID-19 are pandemics that have a severe impact on children and adolescents' well-being, and they interact in a negative way, both physiologically and psychologically. The COVID-19 epidemic had a significant impact on children's everyday lives and the same measurements also had an impact on eating habits, resulting in increased snacking and consumption of treated foods. Unhealthy food, along with a significant piece in physical activity and an increase in sedentary lifestyle, have been linked to weight growth, particularly in children with overweight. Obesity is the most prevalent comorbidity of COVID-19 in children; immunological dysregulation, poor nutritional status and metabolic imbalance may all play a role in the obesity-COVID-19 association (3, 14).

Conclusion

More clinical studies with a larger population and tissue vitamin D levels are needed to determine the true impact on the course of COVID-19 infection. However, up to know the data indicate that vitamin D play an important role in maintaining immune system balance which is most certainly disturbed during the infection. Both in obesity and in the disproportion of vitamin D status, primary prevention plays a key role, and how these two conditions could affect children with covid-19 infection. The connection between obesity, covid-19 and vitamin D is very interesting. Further research in this direction is crucial for a final solution in the fight against current epidemics and overall child health.

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Dr Marković Aleksandar,
18000 Niš, Pariske Komune 3/34
Mail:markovic.aleksandar993@yahoo.com
