

ESPE Physician Information on COVID-19 and Pediatric Endocrine Disease

Disease specific information and advice – Vitamin D deficiency

Introduction

A novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected almost 11,000,000 individuals, claiming more than 500,000 lives in over 200 countries worldwide ever since its outbreak in Wuhan, China in December 2019. The disease then rapidly spread from Wuhan to other areas of China and throughout the world. On January 3, 2020, a novel coronavirus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or 2019-nCoV)—with phylogenetic similarity to the SARS coronavirus (SARS-CoV), the cause of the 2003 SARS outbreak, was isolated in samples of bronchoalveolar lavage fluid from patients in Wuhan and was confirmed as the cause of the novel atypical form of pneumonia [1]. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a public health emergency of international concern [2]. As of July 4 2020, 10,922,324 people have been infected and 523,011 people have died from COVID-19 globally. The virus spreads like any other respiratory infectious disease, through contaminated air-droplets of infected persons when talking, coughing, or sneezing. It can survive in the environment from a few hours to a few days, depending on surfaces and environmental conditions. The mouth, nose, and ocular mucosa appear to be the major way of transmission.

In this review, we present a brief overview of the current knowledge on COVID-19 and its relationship with endocrine diseases, and we make recommendations as Pediatric Endocrinologists managing patients with increased susceptibility to Covid-19.

Introduction. Definition, phenotype and treatment of vitamin D deficiency

More than 80% of vitamin D (VitD) in humans comes from skin synthesis. Unfortunately, environmental and individual factors such as living at higher latitudes, cloud cover and air pollution, darker skin pigmentation, aging and use of sun protection cosmetics could be responsible for insufficient vitD production. Balanced diet could cover the remaining 20% of daily demand for vitD intake. However, in the case of limited skin synthesis, even healthy and varied diet is not able to make up for deficiencies and using appropriate supplements is recommended [3].

VitD status is assessed by measuring blood levels of total 25OHD and its concentration above 20 ng/ml (50 nmol/l) or above 30 ng/ml (according to other recommendation) is considered as sufficient [4].

Despite the availability of vitamin D supplementation and published recommendations for prevention,

vit D insufficiency or deficiency is common worldwide. They could have a major impact on children's development and growth as well as their general health. Similarly to different cut-offs for deficiency definitions there are different recommended therapeutic protocols [3, 4]. The risk groups of VitD deficiency that need individualized prevention-treatment approach (e.g. obese individuals require double dose of VitD supplementation recommended for healthy age-matched peers) are identified and part of them present evident endocrine symptomatology [3]. VitD deficiency has been described as a pandemic. Regardless of age and ethnicity, recent data showed that 40% of Europeans are vitamin D deficient and 13 % are severely deficient [5].

Based on review and meta-analysis of 52 studies the prevalence of VitD concentration below 20 ng/ml in acute and critically ill children was high and associated with increased mortality [6]. Additionally a recently published meta-analysis confirmed that deficiency of VitD in children may have an independent relationship with up to 2.2 fold risk increase of sepsis and acute and critical care unit mortality [7].

Are patients with vitamin D deficiency at increased risk of corona infection and severe course of COVID-19?

For several weeks there has been an increasing interest in the influence of vitD deficiency on the risk, severity and fatality of COVID-19. The number of publications related to COVID-19 risk or severity in the context of VitD deficiency increase rapidly [8]. However, in children and young patients disease course of COVID-19 is generally mild or even asymptomatic, thus almost all observations and statistics refer directly to adult population.

Vitamin D supports production of antimicrobial peptides in the respiratory system, therefore making infection with the virus and development of COVID-19 symptoms less likely. Moreover, vitamin D might help to reduce the inflammatory response to infection with COVID-19. Low vitamin D concentration has been associated with a significantly increased risk of pneumonia and viral upper respiratory tract infections [9].

Vitamin D deficiency plays an important immunologic role and it has been postulated as a determinant of severity of COVID-19 infection [10]. Furthermore, vitamin D deficiency is associated with an increased risk of thrombotic episodes, frequently observed in COVID-19. Some observations confirmed correlation between low levels of vitamin D and the higher frequency of COVID-19 cases and mortality in this infection course. Vitamin D deficiency is found to occur more frequently in patients with obesity and diabetes, both conditions carrying a higher risk of more severe COVID-19 infection [11].

Some data confirmed that vitD deficiency, without sufficient treatment is associated with COVID-19 risk, therefore testing and treatment for vitamin D deficiency is highly recommended [10]. VitD deficiency, confirmed in 13% of American adults, was associated with higher prevalence of hospitalization as well as almost 2-fold higher risk of more severe COVID-19 course. Moreover VitD deficiency, as a comorbidity, indicated as much as a 2.5-fold higher rate of admission to the intensive care unit [12]. The study by Ali (May 2020) found a significant negative correlation between mean vitD levels and COVID-19 cases per one million population in European countries, but not between vitD and deaths due to COVID-19 [13]. Another study with a small sample size also failed to link more severe COVID-19 course to vitD deficiency [14]. Furthermore, a British study with almost 350K adult participants did not support a potential link between vitD concentrations and risk of COVID-19 infection, nor the notion that vitD concentration may explain ethnic differences in COVID-19 infection [15].

In the context of the prevalence of vitamin D deficiency in countries commonly affected by COVID-19 there [16] is a debate regarding the connection between geographic latitudes [17], vitD deficiency and severity of COVID-19 [18]. Typically 'sunny' countries with lower latitude such as Italy (Northern Italy) and Spain, had low mean concentrations of vitD, high frequency of vitamin D deficiency and the highest infection and death rates in Europe. The northern latitude countries (e.g. Norway, Finland) which receive less UVB sunlight, actually had better vitD supplementation, much higher mean vitD concentrations, low levels of deficiency and lower infection and death rates [5].

Do the quarantine measures for patients with vitamin D deficiency differ from the general population? What do we recommend?

The quarantine measures for patients with vitamin D deficiency do not differ from the general population. Besides routine treatment, vitamin D supplementation is recommended in therapeutic doses.

What is the advice on the regular monitoring and therapeutic procedures of patients with vitamin D deficiency?

Little is known about the protective factors of COVID-19 infection. Therefore, preventive health measures that can reduce the risk of infection, progression and severity are desperately needed. Despite the lack of direct evidence of an effect of vitamin D levels on COVID-19 infection, regardless of the age-group, one could assume that vitamin D deficiency is an easily modifiable risk factor and should be actively corrected through safe, inexpensive and easily-available vitamin D supplements. Even a small decrease in COVID-19 infections would easily justify this intervention.

The general rules for vitamin D status monitoring during COVID-19 are in line with recommendations for non-COVID-19 patients. Randomised controlled trials showed that vitamin D supplementation was safe and it protected against acute respiratory tract infection overall [19].

Summary: There is not enough evidence on the association between vitamin D levels and COVID-19 severity and mortality in pediatric population. Our knowledge is based on individual studies performed on adults. From previous studies, published before the COVID-19 era, we know that rate of vitamin D deficiency in acute and critically ill children was high and associated with increased risk of sepsis and mortality. Therefore, well-planned high-quality trials are required. Prophylactic vitamin D supplementation is highly recommended according to guidelines and in case of vitD deficiency therapeutic dose should be proposed.

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