



STÁTNÍ ZDRAVOTNÍ ÚSTAV

## COMED study - high vitamin D levels did not reduce mortality in patients with COVID-19

Preliminary results. The results of a study in patients hospitalized with COVID-19 at the University Hospital Brno focused on the effect of vitamin D on mortality. The conclusion was a bit surprising. High serum/plasma 25OH-D levels in patients (>75 nmol/l) did not lead to a reduction in mortality. On the contrary, very low values < 36.7 nmol/l statistically showed increased mortality.

Another aim of the study was to prevent the development of inflammation through vitamin D or its metabolite in the blood, 25OH-D. It may play an important role in the pathogenesis of COVID-19. A serious complication of this viral disease may be pneumonia (ARDS), observed in up to 30% of cases in moderate and severe patients. The study responded to a campaign by the Ministry of Health aimed at improving lifestyle. We know that the diet of the majority of the Czech population is deficient in anti-inflammatory nutrients. This includes vitamin D.

### Why vitamin D is important

Vitamin D is a well-known hormone. It acts on more than 200 genes, including immune cells. Evidence of its deficiency and the severity of COVID-19 is considerable in the country. Vitamin D shows that it may be important in the regulation and suppression of the inflammatory cytokine response of respiratory epithelial cells, macrophages, and the subsequent acute respiratory distress syndrome, which is usually the cause of death. It helps repair the disrupted pulmonary epithelial barrier and reduces the risk of thrombotic complications.

### Will higher levels of vitamin D reduce mortality?

This study hypothesized whether there is a relationship between vitamin D and mortality/morbidity in patients with COVID-19. We investigated whether higher levels of vitamin D (measured as 25-hydroxy vitamin D), determined in the serum/plasma of hospitalized patients, would correlate with a lower risk of serious complications, especially mortality.

### What the study included

In a collaboration between the SZÚ (NIPH) and the Brno University Hospital, we collected and analyzed 217 "positive cases", based on "COVID+" information, from February to early May 2021. After removing "confounders", a cohort of 160 individuals was statistically analyzed. At the beginning of hospitalization of patients with COVID-19, we collected 25OH-D levels (nmol/L). Blood levels of the vitamin usually plateau in 4-6 weeks. Due to the small number of patients, men and women were not divided. The cohort was divided into quartiles, of 40 patients each, according to the % of serum/plasma 25OH-D levels.

### Epidemiological statistics confirmed higher mortality in low 25OH-D levels

The comparison (deaths/survivors) for the lowest quartile (Q1) was less than 36.7 nmol 25OH-D/l, versus the remaining higher 3 quartiles combined (Q2-Q3-Q4). The difference was statistically significant! Relative risk



(RR) = 0.44 (CI95% = 0.23-0.86), Z score = 2.42, P = 0.016, NNT = 6 (3.3-30.2). Figuratively, one can imagine that 1 in 6 patients will survive if they have more than 36.7 nmol 25OH-D/l. Odds ratio (OR) = 0.36 (CI95% = 0.15-0.85), Z score = 2.34, P = 0.019. Obviously again a conclusive result. There was a statistically significant age difference between the lowest quartile (Q1) and the other higher quartiles (Q2-Q3-Q4), Q1 being slightly higher in age. The results were confirmed after the age standardization of the cohort. Results This result is very interesting because higher 25OH-D levels (above 75 nmol/L) were not shown to have a protective effect in terms of mortality. According to some publications, the effect should be positive. But recent publications confirm our result.

### **What the results of the study mean**

The study was not simply due to a number of poly-morbidities. Initially, patients were given a high dose of vitamin D during hospitalization. To our knowledge, this practice was eventually abandoned. The aim was not to cure, but to determine whether higher high blood doses of vitamin 25OH-D could prevent critical conditions, mortality, in the context of the development of a "cytokine storm" and modulation of the immune system, in the development of severe pneumonia (ARDS). The study is obviously a pilot, but we consider the result consistent.

### **What our population looks like and what to do**

In 2018, the first information on vitamin D saturation in the adult population was obtained as part of the human biomonitoring of the NIPH. Vitamin D metabolites 25-hydroxyvitamin (25-OH-D = 25-OH-D2 + 25-OH-D3) were analyzed in the blood serum of adults. The metabolite 25-OH-D3 was overwhelmingly represented in the total. An adequate supply of vitamin D (measured by serum 25(OH)D concentrations) is not clearly defined. Traditionally, values below 25 nmol/l are considered deficient in Europe. The United States Institute of Medicine's Dietary Reference Panel defines the threshold for risk of inadequate supply as 30 nmol/l. A number of experts consider 50 nmol/l to be a reasonable threshold for adequate supply, but the Endocrine Society's Expert Working Group on Clinical Guidelines Subcommittee recommends serum 25(OH)D levels above 75 nmol/l for disease prevention. Of the total number of adults studied in the Czech Republic (N=403), only 32% had an optimal level above 75 nmol/l. It is known that 25(OH)D levels have a marked seasonal dependence on the intensity of sunlight. A major vitamin D deficiency was observed, as in other studies, in the winter and spring months.

### **Further research, monitoring, and change of legislation**

Determination of 25OH-D levels is of considerable health importance throughout life and is part of prevention. Food levels of vitamin D are relatively low. We believe that the reference value labeled on food should be changed. We have asked for a change in legislation (EPR 1169/2011) in Brussels, but the EC has replied that this is not their priority. So there is a general contradiction between the food labeling (5 ug/person/day) and the new EFSA DRV (15 ug/person/day).