

COMED study: COVID-19 disease and the effect of omega-3 FAs and vitamin D.

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Severe acute respiratory syndrome caused by coronavirus-2 (SARS-CoV-2), responsible for coronavirus disease (COVID-19), is a complication that has spread rapidly worldwide. COVID-19 has caused significant loss of life and disrupted global society. While the disease was predominantly characterized initially by respiratory symptoms, it is understood that other organ systems, including the cardiovascular and nervous systems, may also be affected. These include thrombotic complications, venous thrombosis, vasculitis, cardiomyopathy and stroke. Thrombosis and inflammation are involved in various chronic diseases. This is of great concern because people with pre-existing health problems, or outright multi-morbidities (such as cardiovascular disorders, renal disorders, obesity, metabolic syndrome, diabetes), are logically at greater risk of severe COVID-19 infection. Therefore, research into strategies for the prophylaxis and treatment of COVID-19 is important. Omega-3 fatty acids may also play an important role in the pathogenesis.

At the same time, vitamin D is often added to the body along with omega-3 fatty acids (FAs). It has many mechanisms by which it reduces the risk of microbial infection and death, including the physical barrier, cellular natural immunity and adaptive immunity. Vitamin D supplementation has shown beneficial effects in viral infections including influenza and HIV. The effects of vitamin D supplementation during COVID-19 infection remain controversial. Looking ahead, clinical trials are needed to define better cut-off values for vitamin D levels and ultimately what dosage is best.

Our pilot clinical study in collaboration with SZÚ-CZVP and FN Brno focused on mortality of patients with COVID-19 at higher omega-3 index and vitamin D levels. It was conducted in the period February-May 2021. The abstract summarizes the main findings of the study.

1. Reduced mortality in COVID-19 patients with higher omega-3 index

The study statistically confirmed the hypothesis that a higher value of the so-called omega-3 index (sum of EPA+DHA+DPA¹ /sum of MC in erythrocytes) leads to lower mortality in patients with COVID-19, who usually succumb to pneumonia. This is an encouragement for further work in the field of nutrition and promotion of the inclusion of long-chain omega-3 MK sources in the diet (not to be confused with essential ALA², although this is also of great importance).

One of the aims of the study was to prevent chronic inflammation. Omega-3 FAs are important, especially EPA and DHA, but also DPA. They may play a role in the pathogenesis of COVID-19. A

¹ EPA - eicosapentaenoic acid, DPA - docosapentaenoic acid, DHA - docosahexaenoic acid

² ALA - α-linolenic acid

serious complication of this diagnosis may be pneumonia, observed in up to 30% of moderate and severe cases. 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 these anti-inflammatory nutrients.

What the study included

In cooperation with SZÚ-CZVP and FN Brno we collected and analyzed 217 blood samples of "positive cases", based on their designation as "COVID +". After removal of "confounders", a cohort of 160 persons was statistically analysed. We worked with data on the concentration of 20 different MKs in erythrocytes. This typically represents a time period of at least 2-4 months prior to hospitalization, for blood levels to stabilize. Due to the small number of patients, the cohort was not divided into males and females. The cohort was divided into quartiles, of 40 patients each, according to the % of levels of the sum of omega-3 (EPA+DPA+DHA), in whole blood. Vitamin D values were similarly handled (see below).

Epidemiological statistics confirmed lower mortality

The comparison (deaths/survivors) of the highest quartile (Q4), where $> 6.4\%$ (EPA+DPA+DHA) was found, was statistically significant against the remaining 3 lower quartiles combined (Q1-Q2-Q3)! Relative risk (RR) = 0.23 (CI95% = 0.06-0.93), Z score = 2.06, P = 0.039, NNT = 6 (3.3-30.2) - a patient figuratively survives 1 : 6 if he/she has more than 6.4% EPA+DPA+DHA in venous blood. If capillary blood values are measured, the values are multiplied by 0.78. Odds ratio (OR) = 0.19 (CI95% = 0.04-0.84), Z score = 2.19, P = 0.029. This is a conclusive result. There was no statistically significant age difference between Q4 and the other quartiles, obviously after statistical age standardization.

What the study results mean

The study was not simple, due to a number of polymorbidities. It was not about cure, but to see if a higher omega 3 index could prevent critical conditions, mortality, in the context of a "cytokine storm" preceded by an "eicosanoid" storm, in the context of pneumonia. The study is of course a pilot, but the result is consistent.

What our population looks like and what to do

The value of the omega-3 index, which in our case we increase by DPA (it is about 20-23% of omega-3, excluding ALA), should be $> 8.0\%$. Almost no one in our population has this value. The value can be achieved if the diet is based on high doses of fatty fish (salmon, snapper, mackerel, sardines, etc.). But otherwise there is only one way and that is to use fish oil, which is sold in many varieties. In our experiments (note legal contract with SZU, Vitana/Orkla) we use triglycerides from Mollers (Norway).

2. High vitamin D levels did not reduce mortality in patients with COVID-19

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. Pneumonia can be a complication of this viral disease, seen in up to 30% of cases in moderate and severe patients.

Why vitamin D is important

Vitamin D is a well-known hormone. It acts on more than 200 genes, including those affecting immune cells. Evidence of its deficiency and the severity of COVID-19 is considerable in the Czech Republic. 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 vitamin D levels reduce mortality?

The 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 blood serum of hospitalized patients would correlate with a lower risk of serious complications, especially mortality.

What the study included

We worked with the same group of patients where the omega-3 index values were measured. In collaboration with SZÚ-CZVP and FN Brno, we collected and analyzed serum samples from 217 "positive cases", designated as "COVID+", from February to the beginning of May 2021. After removing "confounders", a cohort of 160 individuals was statistically analyzed. At the beginning of the hospitalization of the COVID-19 patient, we measured 25OH-D levels (nmol/L). Blood levels of the vitamin usually plateau in 4-6 weeks. Due to the small number of patients, males and females were not divided. The cohort was divided into quartiles, of 40 patients each, according to the % of serum 25OH-D levels.

Epidemiological statistics confirmed higher mortality at low levels of 25OH-D

The comparison (deaths/survivors) for the lowest quartile (Q1) was less than 36.7 nmol 25OH-D/L, compared with 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 was slightly higher in age, but the results were conclusive after statistical age standardization. The 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 study results mean

The study was not simple due to a number of polymorbidities. 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 high doses of vitamin 25OH-D in the blood could prevent critical conditions, mortality, in the context of the development of a "cytokine storm" and modulation of the immune system, and in the context of the development of severe pneumonia (ARDS). The study is obviously a pilot, but we consider the result to be consistent.

What our population looks like and what to do

In 2018, the first information on the vitamin D saturation of the adult population in the human biomonitoring SZU. The metabolites of vitamin D - 25-hydroxyvitamin (25OH-D = 25OH-D2 + 25OH-D3) were analyzed in blood serum of adults. The metabolite 25OH-D3 was overwhelmingly represented in the total. Adequate supply of vitamin D (measured by serum 25OH-D sum 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. The Expert Panel considers a reasonable cut-off value for

sufficient supply of 50 nmol/l, however, the Expert Working Group of the Endocrinological Society's Clinical Guidelines Subcommittee recommends serum 25OH-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 value above 75 nmol/l. It is known that 25OH-D levels have a marked dependence on the season related to the intensity of solar radiation. A major vitamin D deficiency was observed, similar to other studies, in the winter and spring months.

Further research and monitoring

Determination of 25OH-D levels is of considerable health importance throughout life and is part of prevention. Vitamin D levels in food are relatively low. We believe that the reference value labelled on food. We asked for a change in legislation (EPR No.1169/2011) in Brussels, but the EC replied that this is not their priority. So there is a general contradiction between the food labelling (5 µg/person/day) and the new EFSA DRV (15 µg/person/day).

Motto: *Lifestyle and health care is a serious task for all of us. Unfortunately, this is not yet very well promoted in our population, but the situation will surely change over time. When asked by journalists what the epidemiological statistics mean, we can, of course, answer figuratively... if about 30000 people died of COVID-19 in the Czech Republic, theoretically over 5000 people could have survived severe pneumonia if they had followed the nutritional recommendations... this is the entire population of the spa town of Luhacovice... we need to reflect on this reality.*

Basic literature

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