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Immune System

Long-term Effects of COVID-19

What Can Biofactors Do in Long- and Post-COVID

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Vitamins, minerals and trace elements – they all ranks as biofactors that play an important role in a wide variety of diseases due to their physiological functions. While studies have shown positive effects of some biofactors such as zinc and vitamin D_3 in SARS-CoV-2 infection, there is hardly any valid data for patients with Long-COVID or Post-COVID. The following article sheds light on the topic in an evidence-based manner and still gives some practical therapy recommendations.

"*The guideline recommendation of the **British National Institute for Health and Care Excellence**, already published at the end of 2020, defines **Long-COVID** as health complaints that persist or recur beyond the acute disease phase of a SARS-CoV-2 infection of four weeks. **Post-COVID Syndrome** refers to symptoms that are still present more than twelve weeks after the onset of SARS-CoV-2 infection and cannot be explained in any other way*, "accordingly also reads the definition of the **Robert Koch Institute** [1].

Long-COVID or Post-COVID?
In studies and analyses cited in this post, the terms Long-COVID and Post-COVID are actually not used uniformly or the examinations were carried out at different times after the SARS-CoV-2 infection of the patients. Increasingly, but not consistently, the above-mentioned definition of the RKI is used.

How Many Patients Are Ill?

According to statistics, between ten and 35 percent of those affected suffer from symptoms, sometimes long after their corona infection. How high the number actually is, however, can only be guessed. This is partly due to the fact that the definition of Long-COVID or Post-COVID is not used consistently in the scientific studies and/or the studies have methodological weaknesses such as lack of control groups or do not take into account differences in the age and previous health status of the patients.

According to an analysis from the USA, the risk of long-term consequences of a SARS-CoV-2 infection is still "greatly overestimated" [2]. However, this analysis is viewed very critically by other scientists and is themselves classified as flawed. A large part of science and medicine therefore takes the clinical picture seriously. And even though the exact number of sufferers is not known, research assumes the fact that it does not concern a uniform clinical picture, but rather different long-term health consequences that affect different organ systems and cause different symptoms:

- Shortness of breath, cough
- Performance weakness
- Concentration and memory problems
- Sleep disorders
- Fatigue, chronic fatigue syndrome (CFS)
- Muscle weakness and pain
- Pain and discomfort in the nerves
- Depression and anxiety
- Disturbances of taste and smell

According to a survey of patients up to 24 months after corona infection published in July 2023, the most common complaints were:

- Fatigue (34.8%)
- Amnesia (30.3%)
- Difficulty concentrating (24.2%)
- Insomnia (20.5%)
- Depression (19.7%)

And although neuropsychiatric quality of life improved over time, it continued to affect 32.7 percent of subjects [3].

Charité Study on Post-COVID

"*Many people have problems with breathing, difficulty concentrating, or little to no stamina. A large proportion of people with Post-COVID syndrome (PCS) complain of fatigue, which hardly improves with normal rest and recovery. In many cases, these people therefore struggle to cope with daily life, and even mild exertion aggravates their condition, a phenomenon known as exercise intolerance,"* according to a statement on Charité's website – which also mentions a study of more than 100 PCS patients who still suffered from severe fatigue and exercise intolerance six months after contracting SARS-CoV-2. *"Unfortunately, our data show that people with Post-COVID Syndrome who suffer from severe fatigue are still sick more than one an a half years after the initial infection,"* said ***Dr. Judith Bellmann-Strobl***, senior physician at the **Experimental and Clinical Research Center**, a joint institution of Charité and the **Max Delbrück Centers**. *"Only half of them – the half who don't have the full spectrum of symptoms of ME/CFS (ME: Myalgic Encephalomyelitis) – experience gradual improvement in at least some symptoms."*[4, 5]

The PreVitaCOV Study

Assuming autoimmunological and chronic inflammatory processes, drug treatment with prednisolone and neurotropic B vitamins is being investigated [9, 10]**.**

PreVitaCOV is one of the first drug therapy studies on the topic of Post-COVID syndrome in Germany. The randomized placebo-controlled pilot study started in February 2022 and should investigate the efficacy of prednisolone and vitamins B_1, B_6 and B_{12} alone or in combination for two years. The University Hospitals of Würzburg, Tübingen and Schleswig-Holstein as well as the Brandenburg Medical School are examining whether symptoms such as fatigue, shortness of breath, difficulty concentrating, anxiety or depression can be alleviated by the combined treatment. The background to this is the hypothesis that nerve inflammation is the cause of these complaints. "*The common neurological symptoms in Long- and Post-COVID suggest treatment with certain B vitamins that support the nervous system. However, the effectiveness of such treatment approaches has not yet been scientifically proven. The PreVitaCOV project aims to close this gap*," explains the Federal Ministry of Education and Research, which funded the study [11].

What do these connections mean in practice? Even if study results are lacking, a therapy experiment with the aforementioned B vitamins could be undertaken with affected patients – with good knowledge of vitamin B deficiency symptoms [12] and laboratory diagnostics [13].

Biofactors and Long-/Post-COVID?

A lot of research is being done, but there is currently no treatment that tackles the cause of Long-/Post-COVID itself. This is partly due to the fact that various hypotheses are being discussed as to what processes take place in the body [6, 7]. The treatment therefore has the objective of alleviating the symptoms; and inevitably, such symptomatic therapy cannot be limited to compensating for a potential biofactor deficiency. And the experimental, blanket supplementation of dietary supplements with as many vitamins, minerals and trace elements as possible does not correspond to the scientific data and can therefore not be recommended. Paramount rather is supplementation adapted to the clinical picture and the individual needs of the patient, thus also the targeted use of individual, also scientifically tested biofactors, which could supplement and support the therapy as approved drugs. Since the clinical picture of Long- and/or Post-COVID is still comparatively young, there is still little data available at this point in time – mainly from intervention studies, that means from studies in which the use of supplementation of individual biofactors were investigated.

What Role Does Vitamin B_{12} Play?

Many symptoms of Long- and Post-COVID correspond to symptoms of vitamin B deficiency. The possible explanation is that the virus damages nerves, which can trigger various neurological complaints. B vitamins have a close connection to the nervous system and a corresponding deficiency could have a negative effect. "*This [...] Vitamins are partly responsible for a healthy nervous system in many ways, because they are needed for both brain and nerve metabolism as well as for the development of nerve cells. This makes B vitamins ideal companions for Post-COVID symptoms of a neurological nature*," this or similar recommendations are therefore also made on various Internet platforms [8].

However, no corresponding studies have been published so far – neither observational nor intervention studies.

What could other biofactors do?

If you look at the symptoms of Long- and Post-COVID and compare them with the deficiency symptoms of some vitamins and minerals, these biofactors could also be beneficial.

- Disorders of the immune system, increased susceptibility to infections: Vitamins C and D_3, zinc
- Muscle weakness and pain: magnesium, Vitamins C and E
- Fatigue, CFS: Magnesium, Vitamin C
- Depression and anxiety: magnesium, Vitamin D_3
- Reduced sense of smell and taste: Zinc

However, before any of the biofactors mentioned above are used, it is important to consider the following:

1. To date, there are no evidence-based data on their effectiveness in Long-/Post-COVID symptoms.
2. A therapy trial should only occur if the respective deficiency symptoms of the biofactors used are well known and under laboratory control.
   For more information, please visit: www.gf-biofaktoren.de.

What Role Does Vitamin D_3 Play?

The occurrence of Long-COVID is associated with Vitamin D_3 deficiency – according to the results of a study on the Vitamin D_3 status of 100 patients, half of whom showed Long-COVID symptoms, the other half did not [14]. According to the study's authors, COVID-19 survivors with Long-COVID had significantly lower 25(OH) Vitamin D_3 serum levels compared to patients without Long-COVID [13]. Particularly low values were found in the presence of neurocognitive complaints. In addition, lower levels of 25(OH) Vitamin D_3 were found to be the only variable significantly associated with Long-COVID. The scientists recommended that Vitamin D_3 status in COVID patients be regularly checked after hospital discharge and tested for the potential use of Vitamin D_3 supplementation as a prevention against Long-COVID.

The links between Vitamin D_3 deficiency and Long- and/or Post-COVID have also been proven in other studies [15]. However, intervention studies are still pending.

Conclusion for the Practice?

Even if quite a few patients suffer from Long- and/or Post-COVID, the overall study situation is still thin and there is little well-founded data on the topic of biofactors in particular. A correlation between Vitamin D_3 deficiency and Long- and/or Post-COVID has been demonstrated.

With regard to the potential benefit of Vitamins B_1, B_6 and B_{12}, the physiological relationships in the nervous system suggest that a therapy experiment should be started. The use of other biofactors such as magnesium, zinc or Vitamin C can be evaluated with similar caution in the case of corresponding deficiency symptoms.

Keywords: *Biofactors, Corona, Immune systems, Long-COVID, Orthomolecular Medicine, Post-COVID, SARS-CoV-2*

Short interview with *Prof. Dr. med. Klaus Kisters*,
internist and deputy chairman of the Society for Biofactors (GfB)

Prof. Kisters. In your opinion what needs to be considered with regard to Vitamin D_3 in patient care?
Kisters: In general, I consider it important to pay specific attention to biofactor care in practice, but at the same time to avoid self-medication by the patient. This is especially true for Vitamin D_3. The positive effects of the biofactor are not only very present with regard to a potential use in Long- and/or Post-COVID. Occasionally, you cannot get rid of the feeling that Vitamin D_3 helps against everything and that every patient would benefit equally from supplementation. In practice, however, it is important to look at the studies and use the biofactor where there is a deficiency or where health effects are documented.

Additionally, it is not valid that: a lot helps a lot. I consider the intake of very high doses of Vitamin D_3, which are often in the range of several tens of thousands of international units, to be negligent without laboratory control. Vitamin D_3 is a lipid-soluble vitamin, so D hypervitaminosis cannot be ruled out.

How should the therapist proceed in case of suspected Vitamin D_3 deficiency and/or in high-risk patients?
In this case, targeted laboratory diagnostics are recommended. In order to obtain indications of the Vitamin D_3 supply, the Vitamin D_3 serum level is not measured, as this only reflects the intake of the last few days. In order to determine the long-term supply of the biofactor, the storage form calcidiol is measured with the chemical formula $25(OH)D_3$. In agreement with the U.S. Institute of Medicine and the WHO, the DGE considers a serum calcidiol concentration of at least 50 nmol/l or 20 ng/ml to be the concentration that reflects a desirable Vitamin D_3 supply.

However, there is currently some discussion about Vitamin D_3 diagnostics. On the one hand, in 2022, a consensus of experts recommended slightly higher reference values. Another topic is the so-called free Vitamin D_3, which reflects the actual biologically active status of the biofactor. However, this measurement is not yet routinely offered by all laboratories.

As you can see, this is not the last word. However, calcidiol levels above 125 nmol/l or 50 ng/ml should be avoided in all cases because they increase the risk of hypercalcemia.

Can you give any tips on supplementing with Vitamin D_3?
In conformity with scientific studies, supplementation should take place only in cases of proven Vitamin D_3 deficiency and then in daily doses between 1,000 and 4,000 IU of Vitamin D_3. In the case of absorption disorders or obese patients, and in order to achieve rapid correction of Vitamin D_3 deficiency, higher doses of Vitamin D_3 up to 6,000 IU per day can be used for the first four to twelve weeks of treatment. Thus also according to the recommendations of the expert consensus cited above, on which, by the way, ***Prof. Stefan Pilz***, Vitamin D_3 expert and member of our society's scientific advisory board, contributed.

And perhaps another hint: a Vitamin D_3 deficiency often occurs at the same time as a magnesium deficiency. Then both biofactors should also be supplemented. For magnesium, the daily doses are 300 milligrams, possibly a little higher.

Thank you very much for the interview, Prof. Kisters.

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Dr. Daniela Birkelbach. She worked actively in the pharmaceutical sector for many years in the area of vitamins and minerals as a lecturer and editor. In 2014 she became self-employed as a *Heilpraktiker* (naturopath) in her own practice with the main focuses of acupuncture, phytotherapy and nutritional counselling. Within the framework of her nutritional advice for her patients she attached great importance to the supply with biofactors, above all vitamins and minerals. Since 2019 she has supported the public relations work of the Society for Biofactors e.V. (GfB) which is based in Stuttgart.

Prof. Dr.med. Klaus Kisters worked until the end of 2022 as Chief Physician at the Medical Clinic I at St. Anna Hospital in Herne, where he headed the excellent Hypertension Center, as the European Hypertension Excellence Centre (ESH). Since January 2023, he has been deputy head of the Herne Dialysis Center. Since 2001 he has been a professor at the University of Münster. His numerous scientific research papers, especially on magnesium, are documented in over 160 publications in the US National Library of Medicine. He is Vice President of the Gesellschaft für Magnesiumforschung [Society for Magnesium Research] and Vice President of the Gesellschaft für Biofaktoren e. V. [Society for Biofactors]. In 1999 he received the Advancement Award of the Society for Magnesium Research and in 2017 the Trace Award.