Vitamin D – central pillar for the immune system – latest research findings

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Introduction

Vitamin D deficiency is perhaps the most widespread vitamin deficiency in the world. Leading researchers in the field refer to this as a hidden epidemic that may lead to hundreds of thousands of premature deaths worldwide each year. A study conducted in Germany came to the conclusion that about 18,000 lives could be saved in Germany alone if the official bodies could decide to recommend vitamin D supplements generally. [1, 2]

The importance of vitamin D has come into sharper focus in the wake of the COVID-19 pandemic, when numerous studies from around the world have consistently shown that the risk of contracting COVID-19 and the risk of a severe progression correlate directly with vitamin D levels. [3, 4] Again, it is believed that widespread supplementation in the population could have saved tens of thousands, perhaps hundreds of thousands of lives. At-risk groups in particular can be protected by vitamin D, as trials in retirement homes have impressively shown. [5]

However, vitamin D does not only show enormous potential with regard to viral infections. Vitamin D3 does not act like an ordinary vitamin in the body, but is converted into a hormone that controls about 2000 genes in the human body. In particular, it is not only one of the central control hormones of bone metabolism and the immune system, but also has far-reaching effects on the nervous system, the cell cycle and many other important areas of health.

Vitamin D is primarily a preventive nutrient. Unlike some other nutrients, there have been few acute uses of vitamin D, such as in the treatment of viral diseases and autoimmune disorders. However, vitamin D can play a more central role in preventing a whole range of diseases and has far-reaching systemic and long-term effects.

In this presentation, I would like to show you an understanding of the mode of action of the hormonal vitamin D system, provide you with orientation as to how current findings on vitamin D are to be classified, and which questions are as yet unanswered.

Vitamin D deficiency

Vitamin D is an unusual vitamin in two ways. First, as already described, it is not so much a vitamin as a hormone precursor. The body uses vitamin D to produce the hormone calcitriol, which is very similar to our body's own steroid hormones.

Secondly, we rely on the sun, not food, for our supply of vitamin D. Vitamin D is the only known nutrient that is formed by exposure of the skin to sunlight and for which food sources play virtually no significant role. This means that sunlight, like water and solid food, is indeed one of our basic daily needs.

It is therefore easy to explain the widespread prevalence of vitamin D deficiency, which can affect up to 80% of the population, as studies have shown. [6–8] Not only do we avoid the sun virtually all day due to our modern lifestyles, but in areas of northern Europe, sunlight is also too low during the winter months to stimulate vitamin D production at all. [9]

North of Rome, significant production of vitamin D only takes place between March and October, and only between about 10 am and 4 pm. Since these times of day correspond to most people's working hours, the majority of people do not get enough sunshine to meet their vitamin D needs almost all year round. [10]

We need to remember that while our lifestyle has changed radically over the last 1000 years, our biology has not. Our bodies are still adapted to a life in subtropical regions and a lifestyle that we can only observe today among very few indigenous peoples: abundant sunshine with most of the time spent outdoors, plentiful exercise and very light clothing that usually leaves more than 70 per cent of the skin directly exposed to sunlight.

Our modern way of life is virtually the complete opposite of the lifestyle to which we are biologically adapted. This leads to significant problems in many areas, and vitamin D deficiency is one of them.

The vitamin D system

Vitamin D is a hormone precursor and is metabolised in the body in various conversion steps to become an active hormone. There are three main forms of vitamin D that are central to this system:

- The vitamin form: vitamin D3 (cholecalciferol)
- The transport form: 25-hydroxyvitamin D3 (calcidiol)
- The hormone form: 1,25-dihydroxyvitamin D3 (calcitriol)

In addition to these three forms of vitamin D, however, there are a number of other components in this system:

- Special enzymes that convert vitamin D into its active form or break it down.
- The vitamin D receptor on the cells by means of which vitamin D develops its effect.
- Messenger substances and hormones such as PTH (parathyroid hormone), which regulate the conversion.
- A number of important micronutrients as cofactors.

Like all hormones, vitamin D is subject to a complex regulatory system, which we will take a closer look at presently.

However, to make matters even more complicated, vitamin D works in two fundamentally different ways:

1) **The endocrine route**
   In this case, conversion of vitamin D takes place centrally in the liver and kidneys. This pathway is tightly regulated by calcium and various hormones and messenger substances.
2) **The autocrine / paracrine route**
   Here, conversion takes place independently and individually directly in the cells and is controlled by local events in the affected tissue.

The endocrine route

The better known of the two pathways is the endocrine vitamin D system, which primarily serves to regulate calcium levels and bone metabolism.

With the **endocrine pathway**, vitamin D formed by the sun is converted in a first step in the liver to the transport form 25-hydroxy-vitamin D3 (25-OH-D3), most of which binds to the transport molecule DBP and thus circulates through the body. In a second step, the active vitamin D hormone calcitriol is finally formed from this circulation form in the kidney.

Both conversion steps are subject to hormonal regulation, which depends on calcium concentration in the blood and is controlled by the parathyroid hormone. The regulation is dramatically shortened as follows: if the calcium level in the blood drops, more parathyroid hormone is released. This ensures a higher conversion of vitamin D to the active hormone calcitriol. By binding to the VD receptor, calcitriol on the one hand causes increased calcium absorption in the intestine and at the same time reduces the secretion of the parathyroid hormone. [11]

The amount of active vitamin D hormone is hence controlled in this case – through a diversion via the parathyroid hormone – by the level of calcium and magnesium in the blood.

All the components of the endocrine vitamin D system, however, in turn depend on certain nutrients as cofactors. Recent research shows that, in the absence of these cofactors, vitamin D is not only ineffective, but can also have negative consequences such as chronic inflammation. [12]

The reason why this is explained below.

Vitamin D and magnesium
Vitamin D must first be converted by the body in various metabolic steps before it can become effective. This conversion requires special enzymes that only function when sufficient magnesium is present.

Vitamin D metabolism therefore comes to a complete standstill at eight points if insufficient magnesium is available. [13]

A review paper from 2019 recently summarised these relationships very well, concluding [14]

"Magnesium is essential for the metabolism of vitamin D, and taking large doses of vitamin D can lead to severe magnesium depletion. Adequate magnesium supplementation should be considered an important aspect of vitamin D therapy."

Vitamin D ineffective without magnesium

Fortunately, this correlation is receiving increasing attention from the scientific community. [15–17] A number of studies have shown that it is very difficult to correct vitamin D levels by taking vitamin D supplements when there is a magnesium deficiency. [18–21]. When there is a magnesium deficiency, the vitamin form simply cannot be processed into the other forms and remains ineffective.

Conversely, it was possible to improve vitamin D levels by correcting a magnesium deficiency without taking any greater amount of vitamin D. [18, 22, 23]

These results testify to the central importance of magnesium for vitamin D metabolism.

Magnesium deficiency due to high doses of vitamin D

However, the connection works in both directions. Vitamin D remains partially ineffective without magnesium, but the intake of high-dose vitamin D can conversely also lead to a magnesium deficiency.

This has far-reaching consequences, as magnesium is an absolutely central nutrient for almost all functions of the body. Magnesium is essential for more than 600 enzyme systems and thus plays a key role in our metabolism.

That's why Dr Carol Dean, in her best-selling book "The Magnesium Miracle", warns against taking vitamin D without magnesium. [24]

"Vitamin D can over-consume magnesium, block and displace magnesium, lead to excessive calcium intake, (which promotes calcification) and can drive people into magnesium deficiency."

The conclusion from these studies is that vitamin D should always be taken together with magnesium if magnesium status is unclear.

Boron – The neglected trace element with a great effect

The trace element boron also has an effect on hydroxylases – but this time on the degrading enzymes that in turn destroy the vitamin D storage form. It is only when both the formation and breakdown of 25-hydroxy-vitamin D3 take place in a controlled manner that the body can properly regulate vitamin D levels. A sufficient amount of boron is necessary here to avoid excessive decomposition of 25-OH-D3. [25] Similarly, it is important to prevent too high a calcitriol value or an unfavourable ratio between calcidiol and calcitriol.

Vitamin D and calcium

One of the central tasks of vitamin D is the regulation of calcium absorption in the intestine. The active vitamin D hormone promotes the absorption of calcium, and the higher the level of active vitamin D, the higher the rate of calcium.

This regulation takes place via the so-called parathormone. A fall in calcium levels in the blood leads to an increase in the release of parathyroid hormone. This results in increased conversion of vitamin D into its hormone form, which in turn increases calcium absorption in the intestine.

This regulatory mechanism can lead to problems when too much, but especially when too little, calcium is ingested. When vitamin D is taken in high doses and at the same time calcium intake is insufficient, the active vitamin D hormone will be greatly up-regulated. The high level of vitamin D and the greatly increased parathyroid hormone cause levels of the active vitamin D hormone to rise and remain elevated over a long period. Since no calcium can be absorbed in the intestine as none is supplied in food, vitamin D levels do not return to normal, but instead remain chronically elevated.

So with a calcium deficiency and at the same time high vitamin D substitution, we have a very high level of parathormone and at the same time a very high level of active vitamin D hormone. This has more negative than positive consequences.

1) It promotes calcium absorption in the intestine,
2) It dissolves calcium from the bones,
3) It increases the influx of calcium into cells. [11]

A positive effect is the stimulation of calcium absorption in the intestine. On the negative side, however, the body begins to dissolve calcium from the bones and this despite the fact that vitamin D is taken in high doses.

What is even more worrying, however, is the fact that the high level of active vitamin D also increases calcium influx into cells. This leads to severe cellular inflammation in the long run. At the same time, cells also begin to pump magnesium and potassium outwards to maintain intracellular electrolyte balance, resulting in intracellular potassium and magnesium deficiency, even when sufficient magnesium is present.

It is therefore important to take sufficient calcium during a high-dose vitamin D therapy, as otherwise the active vitamin D in the blood increases too much, which paradoxically leads to bone damage and chronic inflammation, although vitamin D actually has a positive effect on bones and inflammation.

Since magnesium also regulates PTH levels, it is important to ensure that both minerals are supplied in a calcium-magnesium ratio of 1:1 to 2:1. A balance of magnesium and calcium is necessary in order to regulate the parathormone in a reasonable way and to achieve a healthy vitamin D status. [26]

Practice has shown in this case that there is an ideal ratio of active vitamin D hormone to 25-OH-D3, which can only be correctly adjusted through the simultaneous administration of vitamin D, calcium and magnesium. [12]

Zinc and vitamin D

Vitamin D acts via a special vitamin D receptor (VDR) to which the active vitamin D docks, thereby mediating its effects on cells. An essential component of this VDR is a zinc molecule. The formation and function of the VDR can be impaired if zinc is deficient. Cell tests have shown a clear dose-dependent increase in vitamin D activity as a result of zinc supplementation. [27]

Vitamin A

Vitamin A and vitamin D are antagonists as well as cofactors. This is because activated VDR does not work alone, but combines with the RXR receptor activated by vitamin A to form a so-called heterodimer. It is only when this compound is present that some of the effects of vitamin D become possible. [28–32] When vitamin A is deficient, VDR cannot exert its full effect despite activation by vitamin D. In this case, we also speak of a vitamin A-induced receptor blockade, although it is actually not the receptor that is blocked, but only its effect. This can lead to similar problems as discussed above. Due to the lack of effect, the regulating feedback in the regulatory loop remains absent and the vitamin D hormone remains at a high level over an extended period.

At the same time, vitamin D and vitamin A are also antagonists. Both vitamins activate the retinoic acid receptor (RAR) and are in direct competition. A balance of these two vitamins is therefore crucial in order to maintain a healthy regulation of the vitamin D system.[32–34]

Vitamin K2

Lastly, it is imperative to mention vitamin K2. Although this vitamin plays no direct role in vitamin D metabolism itself, it does play a role in calcium metabolism. It ensures that calcium is removed from the blood and incorporated into bones. Without K2 (MK7 all-trans), calcification of tissues and organs can occur, meaning that K2 is also a useful co-factor in this context. [35–38]

It is often claimed that vitamin D would be ineffective without vitamin K2 – but this is incorrect. Vitamin K2 (unlike magnesium, for example) does not play a direct role in vitamin D metabolism. Vitamin D is thus fully effective and fulfils its task even without vitamin K2 – only this may not be such a good thing if K2 is deficient.

This is because one of the functions of vitamin D is promoting calcium absorption in the intestine. Calcium absorption increases, particularly in the case of high-dose vitamin D therapy and a simultaneous high calcium intake, and this therefore increases the amount of calcium in the bloodstream.

And it is precisely here that vitamin K2 comes into play: because if calcium is to be correctly utilised, transported and incorporated into bones, it needs certain transport proteins – and these in turn need vitamin K2 to become active. [39]

Calcium therefore remains unused in the blood when K2 is deficient and this can cause damage in the body. As calcium plaque, it accumulates in vessels and organs, which can have serious long-term consequences such as arteriosclerosis and coronary heart disease. [35, 40–44]

Or free calcium may combine with oxalate – one of the most common causes of kidney stones.

A number of studies have now shown that the risk of kidney stones increases with high vitamin D levels and decreases significantly with a better supply of vitamin K. [45–48]

Healthy for bones: Vitamin D and K2

The combination of vitamin D and vitamin K2 not only prevents harmful calcification, but is also the perfect combination for our bones and teeth. [38]

Vitamin K2 is required for the activation of three important proteins of the calcium and bone metabolism:

- *Matrix Gla protein*
  Binds and transports free calcium
- *Osteocalcin*
  Plays a role in the incorporation of calcium into bones and teeth
- *Protein S*
  Is a component of the bone matrix

While vitamin D regulates the absorption of calcium for our bones, vitamin K2 is actually the "silent hero" and makes a significant contribution to ensuring that the absorbed calcium does not harm the body, but instead reaches where it is needed: in our bones and teeth. [39, 49–52]

A supply of all central cofactors is therefore important for healthy vitamin D regulation in the endocrine route.

We have taken this into account with our product "Vitamin D Homeostasis", which combines all elements of the vitamin D system in a single preparation that is perfectly coordinated.

The paracrine route

While in the endocrine pathway the conversion of vitamin D into its storage and hormone forms takes place centrally in the liver and kidney, it has been shown that many cell forms can also convert vitamin D into its active forms independently.

This is quite plausible, as our body needs a way to control the level of active vitamin D for immune functions, for example, independently of the calcium supply.

It is believed that the conversion of vitamin D for all non-calcium dependent functions occurs directly in cells, allowing various tissues to self-regulate their levels of active vitamin D.

It has been shown that almost all cell types can produce the enzymes necessary for the conversion of vitamin D themselves, and can thus produce all forms of vitamin D and also break it down.

The "free hormone" hypothesis

There is currently a great deal of controversy regarding the question of which form of vitamin D is used as the starting material. Is it native vitamin D or free 25(OH)D? It was previously assumed that cells use circulating 25-OH-D as the starting material for intracellular conversion to calcitriol – which is why this is currently used as the sole measure of vitamin D supply.

However, almost all 25-OH-D in the blood is bound to vitamin D-binding protein (DBP for short) for transport – and cannot diffuse well into cells in this form. Only a very small

fraction of the 25-OH-D is present in a free form that can easily diffuse into cells and thus be considered a starting material for conversion within the cell.

Studies have shown, for example, that immune cells can produce significant amounts of vitamin D hormone from 25-OH-D in vitro. However, this is no longer possible the moment DBP is added. [53]

Since every person has different levels of DBP, and this also exists in different genetic variants, it is currently unclear as to how meaningful it is to measure 25-OH levels on their own. Various new markers are at present being tested; in addition to 25-OH-D, free fractions are now also being measured either directly or inferred from levels of DBP in relation to 25-OH-D. It is still unclear which markers are relevant here. [54]

These questions have major implications for our understanding of vitamin D and, more importantly, for treatment and could call into question much of the research that has been carried out on vitamin D to date.

On the one hand, these considerations could mean that previous markers are inadequate. Many studies would then be analytically unsatisfactory, since connections are being sought in the wrong places.

But the design could also be compromised, for example if it turns out that 25-OH-D is the decisive marker only for calcium homeostasis, but that free, native vitamin D is key for all other functions. Unlike all other forms of vitamin D, native vitamin D circulates in large quantities in the bloodstream and diffuses easily into all cells. As such, native vitamin D would actually be the perfect substrate for cellular vitamin D synthesis.

However, this would call into question almost all the research on vitamin D that has been undertaken so far. This is because while 25-OH-D circulates in the blood as a transport and storage form for a very long time, the level of vitamin D drops to zero within 24 hours. As a result, there is only a sufficient supply if vitamin D is administered on a daily basis – as would be the case under natural conditions in the sun.

A daily intake of vitamin D in the range of 2000-6000 IU would then be necessary to maintain the effects of vitamin D on the paracrine pathway.

The problem is that weekly or monthly doses have been used in most clinical trials so far in order to simplify the process. However, the free hormone hypothesis holds that only the endocrine pathway could be sufficiently supplied, while the paracrine pathway would run out of substrate after 24 hours. This would mean that much of the research carried out so far would actually have to be repeated with daily doses.

This question has not yet been fully answered, but in our view it is still highly recommended to focus on daily doses. For one thing, this is more in line with the natural pattern of daily supply via the sun and could also be decisive for the majority of all vitamin D effects.

Open questions in diagnostics

As discussed earlier, these open questions also have a major impact on diagnostics. It is generally agreed that 25-OH-D is probably not sufficient as a marker. Native vitamin D, DBP and free fractions of the individual vitamin D forms cannot be measured in a standardised way today, even though some laboratories already offer this. However, it has not been possible to conclusively establish which markers are really meaningful as long as the metabolism of vitamin D has not been fully understood.

At the very least however, it is recommended that the active vitamin D hormone calcitriol (1,25-dihydroxy vitamin D3) should also be assessed alongside 25-OH vitamin D. Valuable information about the overall state of the vitamin D system can be gained by correlating this additional value with 25-OH-D. This ratio of active vitamin D hormone to storage form is called vitamin D status or VD ratio. The reading indicates whether the vitamin D hormone is properly regulated and the overall system is functioning.

Vitamin D status should always be < 1, ideally around 0.5.

Let us consider an example. The following blood values were determined:

Calcitriol (1,25-(OH)2-D): 60 pg/ml
Calcidiol (25-OH-D): 30 ng/ml
= Vitamin D status: 60/30 = 2

The above values show sharply higher levels of the vitamin D hormone (calcitriol), but do not provide any information about the cause.

Appropriate conclusions can be drawn in connection with other markers such as parathormone. As outlined above, the main causes are usually a lack of cofactors such as calcium, magnesium and vitamin A.

Vitamin D receptor blockade
Another hypothesis is currently the subject of considerable debate. According to some researchers, various chronic infections such as Epstein Barr and Lyme disease can interrupt the signalling pathway of the vitamin D receptor. Some viruses, such as the Epstein-Barr virus, are indeed known to exhibit this ability. [55] It is also plausible in evolutionary terms – presumably this ability developed as a survival strategy, since vitamin D controls some of the key defence pathways against these pathogens.

In these cases, vitamin D status would be greatly elevated with otherwise unremarkable blood levels. A further dose of vitamin D would only lead to an increasingly serious increase in active vitamin D hormone, as the regulating feedback via the vitamin D receptor is absent. The consequence here would also be systemic inflammation.

Discussions are still ongoing about how to deal with such pathologies. As a general rule, it is recommended not to use doses of more than 5000 IU of vitamin D, and in severe cases not more than 2000 IU.

Otherwise, the protocols presented so far by Trevor Marshall and Christian Burghardt differ very considerably and would go beyond the scope of this presentation.

According to these theories, a VDR blockade would always have to be considered if, despite the administration of all cofactors, the value of active vitamin D remains elevated

over an extended period, even though blood values show normal values for calcium and parathyroid hormone. However, the hypothesis of VDR blockade remains controversial and has unfortunately been scarcely investigated in clinical trials.

Vitamin D dosage

One of the greatest areas of contention surrounding vitamin D is the question of the right dosage.

While official bodies such as the European EFSA or the American IOM still stick to far too low and scientifically outdated recommendations of 800 IU per day, researchers have been vehemently protesting these recommendations for several years.

There are many reasons for this. Firstly, the recommendations seem untenable from an evolutionary point of view. Humans can easily produce more than 10,000 IU of vitamin D in the skin in summer sun and swimwear. It seems implausible that the biological requirement and biological self-synthesis are so far apart.

Second, the current recommendations are based solely on data collected in connection with bone health and even in this area they are controversial. However, all non-bone-related areas of action of vitamin D are completely disregarded here; to date, there are no reasonable metabolic markers that could be used to define an optimum level of supply here.

Third, comparisons with indigenous peoples show that they have vitamin D levels almost twice as high as those recommended by official bodies. While the IOM sets a value of 20 ng/ml as the threshold for vitamin D deficiency, most indigenous peoples show values of around 40 ng/ml. While this is not proof, it is a strong indication that these are the physiological levels to which we are adapted through evolution. These data are also supported by animal studies showing levels in this range for all primates closely related to us.

Fourth, it appears that many people require much higher dosages to maintain adequate vitamin D levels.

The consensus of most researchers is currently that daily dosages of between 3000 and 5000 IU should be targeted to achieve levels of between 35 ng/ml and 60 ng/ml.

Here too, however, opinions greatly diverge. In recent years in particular, there has been a movement to recommend very high doses of vitamin D and levels above 60 ng/ml for the prevention and treatment of many diseases. However, most publications here are from the popular science field or are limited to case studies, as little clinical research is currently being undertaken in this area.

It is now certain that vitamin D should be based on body weight or body fat levels. As a rough rule of thumb, **50-60 IU per kilogramme of body weight** can be used as an average maintenance dose. This corresponds to 3500 IU - 4200 IU on a daily basis for a body weight of 70kg.

Vitamin D: response index

Again, however, there are a number of new questions. Numerous genetic variants on the vitamin D receptor and on the transport protein DBP lead to large variances in vitamin D metabolism. Dr Carsten Carlberg was able to demonstrate in this context, based

on epigenetic studies, that people need very different levels and doses to achieve the same epigenetic effects. As in the pharmacological field, it seems possible to divide them into **low, mid and high responders**. This principle can be expected for many substances and apparently also applies to vitamin D. There are people who react very sensitively to vitamin D, where even small amounts are enough to exert an optimum influence on the vitamin D system – they are known as high responders. On the other hand, there are also people who need very large doses of vitamin D in order to achieve the same effect – the low responders.

Around a quarter of the people in the Carlsberg study were low responders and need very large amounts of vitamin D in order for the immune cells to actually be affected. Surprisingly, the study could not find any correlation at all between vitamin D levels and the actual epigenetic response. Some people showed effects at 30 ng/ml that other people only achieved at 80 ng/ml.

Carlsberg recommends a compromise dosage around 4000 IU in winter, which provides a sufficient supply and no oversupply for all people on the response index. According to this research, the official recommendations of 800 IU are only acceptable for absolute high responders and do not even achieve optimum effects in this group.

Vitamin D and COVID-19

The discussion about optimum vitamin D supply again took on a new dimension in 2020 in the wake of the SARS-CoV-2 pandemic. Vitamin D deficiency has been found to be one of the key risk factors for

- Contracting COVID-19,
- Suffering a severe course,
- Requiring intensive care and
- Dying of COVID-19.

At the time of writing, numerous studies have been conducted around the world, all of which paint the same picture and provide a broad basis of evidence. [3] They comprise:

- Demographic studies,
- Clear mechanistic parallels between the effect of vitamin D and the pathophysiology of COVID-19,
- Known evidence from previous studies on vitamin D and related respiratory diseases,
- Evidence from correlation studies of vitamin D levels and infection,
- Evidence from correlation studies of vitamin D levels and disease severity,
- Evidence from intervention studies.

Given this broad body of evidence, it is hard to understand why vitamin D has not been used as an important preventive tool in this pandemic. It becomes all the more incomprehensible when you look at the data from these studies.

The risk of contracting COVID-19 at all is almost halved by sufficient vitamin D levels, as various correlation studies suggest. People with low vitamin D levels showed over 100% higher risk of developing COVID-19.

"SARS-CoV-2 positivity correlates strongly and inversely with circulating 25-(OH)-D levels. This relationship exists across all latitudes, ethnicities, both genders, and all ages." as one of the studies summarised its conclusion. [56]

Vitamin D deficiency also correlates with the severity of the disease. 84% of patients who end up in intensive care have a severe vitamin D deficiency, and even 100% in the <74 age group. [57]

One German study showed that vitamin D deficiency is the single most significant risk factor for severe progression, surprisingly even more so than existing lung disease. Even after adjusting for age, sex, and underlying disease (diabetes, cardiovascular disease, kidney disease, lung disease and cancer), the risk of invasive ventilation was six times higher and the risk of death almost 15 times higher for low vitamin D levels. [58]

These results already suggest that vitamin D may help prevent both Sars-CoV infections and serious outcomes. This would make it extremely useful as a preventive measure, especially for the elderly and other at-risk groups.

This is exactly what further studies then found: preventive supplementation with vitamin D doubled the survival rate of frail and elderly people: 82.5% of participants in the intervention group survived COVID-19, compared with only 44.4% in the comparison group. [5]

However, vitamin D not only has preventive benefits in this connection, but may even be a viable therapy, as initial intervention studies have shown. High-dose vitamin D administered in mild COVID-19 courses resulted in a significant reduction in inflammatory markers and a 100% higher recovery rate at 14 days compared to a control group. [59] In another study, supplementing vitamin D deficient patients with 50,000 IU per day resulted in significantly faster recovery, improved inflammatory markers and reduced need for ventilation. [60]

An extremely high dose of 25-OH-D, which would be roughly equivalent to the administration of 300,000 IU of native vitamin D, resulted in a 25- to 30-fold reduction in the risk of ICU admission in patients receiving the calcidiol intervention, and reduced mortality to 0 in the experimental group. [61]

All these results suggest that vitamin D could have played a pivotal role in combating the SARS-CoV-2 pandemic. Population-wide vitamin D supplementation would not only have significantly slowed the spread of the virus in the population, but also saved thousands of lives. It is sad to consider that possibly nearly half of the people who died from COVID might still be alive if this correlation had received more attention.

Researchers at the Heidelberg University even calculate that up to 9 out of 10 deaths from COVID-19 might be directly attributable to low vitamin D levels. They wrote:

"These results suggest that 87% of COVID-19 deaths are statistically attributable to vitamin D insufficiency and may be preventable by eliminating vitamin D insufficiency. Definitive evidence of causality and prevention of death from vitamin D supplementation

can only be obtained from randomised trials that have now been initiated, but the results of such trials will not be available in the short term. Given the dynamics of the COVID-19 pandemic and the demonstrated safety of vitamin D supplementation, it therefore seems highly controversial, and possibly even unethical, to wait for the results of such studies before taking public health action." [62]

Unfortunately, these appeals have gone unheeded. At the time of this manuscript, the UK is the only country providing free vitamin D to at-risk groups, while all other European countries have failed to take the necessary initiative based on this medical data.

The argument that it is necessary to wait for a sounder scientific basis is all the more implausible when you consider the inadequate scientific basis on which the approval of completely new vaccines was granted in the same year, whereas vitamin D has been well researched and demonstrably safe for years. For any pharmaceutical agent, the study results summarised here would have been almost spectacular and probably would have dominated the news for weeks. There was almost complete media silence regarding COVID-19 and vitamin D.

Conclusion

Vitamin D is still an exciting field of research with many new findings and unanswered questions. Although our understanding of the vitamin D system improves from year to year, we are still far from a complete picture.

As a general rule, the following is recommended from the current perspective:

Diagnosis

1) Both calcidiol (25-OHD) and calcitriol (1.25 OHD) values should always be measured in the blood and vitamin D status (calcitriol / calcidiol) established.
2) Vitamin D status should be at least <1 but preferably 0.5;
3) A status >1 can be highly pro-inflammatory.
4) Adjust the vitamin D level to around 50 ng/ml.

Treatment

1) Consider all cofactors / active partners: magnesium, calcium, vitamin A, zinc, boron, vitamin K2.
2) At least 50-60 IU per kg body weight is needed for a level of 50 ng/ml, often more.
3) Watch out for possible VDR blockage in chronic infections.
4) Always give daily – not weekly – vitamin D doses.

Closing words

Overall, the importance of vitamin D – and micronutrients in general – for the health of the general population is still widely underestimated and sometimes negligently ignored.

Micronutrient deficiencies are not a marginal medical phenomenon but, on the contrary, are at the heart of holistic health promotion. Every year, thousands of people die from the indirect consequences of micronutrient deficiencies, as tragically highlighted by the current pandemic.

It is time for political decision-makers as well as therapists and physicians to finally take a closer look at micronutrients and make them a mainstay of general health care.

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