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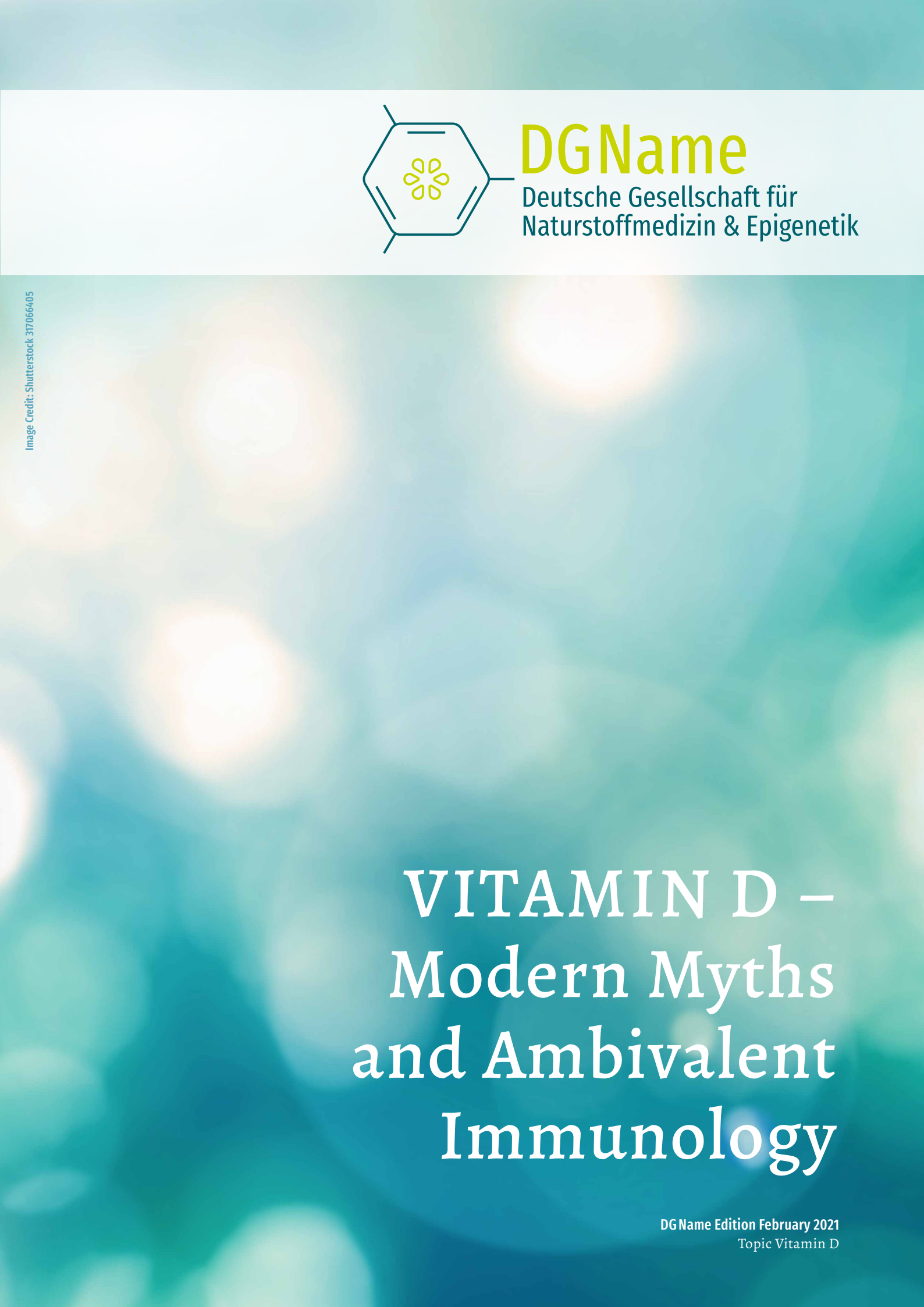

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VITAMIN D – Modern Myths and Ambivalent Immunology

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VITAMIN D – Modern Myths and Ambivalent Immunology

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Content

Introduction

Vitamin D (VitD) has gained enormously in importance and attention over the last 10 years, with no other micronutrient being subject to such a steep increase in research activity, media presence and ultimately, commercialisation. This development and the resulting flood of data – among others at epidemiological, molecular biological, biochemical, (patho)physiological and interventional levels – have resulted in the medical community's fundamental rethink regarding the handling of VitD. This is evident not least by the significant increase in reference values, both for blood levels considered healthy and for recommended daily intake. In a 145-page (!) document, for example, EFSA justifies the increase in the corresponding values by up to 100% *[1]*. Where 25(OH)D blood levels were long considered normal at 20-30 nmol/l, the target serum levels are now specified at >50 nmol/l, with the maximum limit usually extending to 120 nmol/l *[2]*. An estimated 60% of the population is therefore in a status of more or less pronounced insufficiency *[3]*. Especially laboratories specialising in complementary medicine and orthomolecular medicine sometimes use much higher reference ranges of 75-200 nmol/l. This is not least due to the fact that meanwhile, the physiological functions of VitD are defined in a much broader context than in the past. The calcium-phosphate balance was long considered the only essential domain of VitD. This perspective has changed radically with the knowledge gained from human genome sequencing. As a steroid hormone, VitD in its active form acts as a transcription factor, regulating over 1,000 nuclear genes *[4]* and numerous genes in mitochondrial DNA *[5]*. In this respect it is not surprising to find a much broader range of functions than traditionally assumed. As desirable as it is to take this insight into account by adapting the reference ranges – in the author`s view, two not uncritical phenomena have emerged here:

1. The assumption of the VitD metabolism and therefore the questioned usefulness of an intervention could be covered by measuring the serum level of calcidiol in the form of 25(OH).
2. A trend towards »the more, the better«: The increase in maximum VitD levels has, in part, become somewhat grotesque, in particular and primarily calcitriol 1.25(OH)$_2$.

Going beyond its traditional musculoskeletal mode of action, the influence of VitD on the immune system has moved into the focus of interest. Numerous studies have and continue to investigate this connection and now fill entire libraries. PubMed alone lists thousands of corresponding entries, with one aspect in particular coming to the fore: The influence of VitD on our immune system is differentiated, complex and contextual. This already applies to the physiological situation *[6]*, but even more so in the case of a dysfunctional VitD metabolism. This will be the main focus of the following and it will be necessary to show that

3. Simplifications such as »VitD strengthens the immune system« must be strictly rejected.

This is all the more applicable in the current pandemic situation. Although the prophylactic intake of VitD may benefit the immune system, the opposite is equally true: VitD can suppress crucial components of the immune system *[7, 8]*. This is also consistent with decades of practical observation that autoimmune and atopic processes can be favourably influenced by VitD substitution. Irrespectively, VitD can have a contextual pro-inflammatory effect – which is not to be equated with favourable, productive immune modulation. The keyword here being »VDR blockade« (VDR = VitD receptor). Only a differentiated consideration of the VitD metabolism allows a reliable decision at this point and includes the analysis of the following aspects: Central-systemic and peripheral-local regulation of the VitD metabolism, VDR availability as well as VitD's genomic and non-genomic mode of action. Corona in particular shows the full spectrum of these interwoven topics. While low 25(OH) levels increase the risk of infection with SARS-CoV2 *[9]*, immunosuppressive doses of VitD would be of little help in the early phase of such an acute infection. Finally, one of the main dangers of Covid-19 is a hyperinflammatory course – in which case this anti-inflammatory and immunosuppressive VitD administration may be beneficial. In this regard, the art seems to quite obviously be in recognising who needs which VitD substitution and when – and who does not. That this is feasible will be demonstrated below.

The Central and Peripheral Vitamin D Metabolism

THE CENTRAL VITAMIN D METABOLISM

Calcium homoeostasis as a working field for VitD complies with the established textbook knowledge about this micronutrient and was long considered to be the only control loop in which this hormone is integrated. This perspective is also the reason why VitD is attributed an osteoprotective effect, whereby this is a side effect of VitD activity. Under certain conditions, VitD can even have an osteolytic effect (refer to the section »VDR blockade«). The associated physiology is impressively simple at first. A decrease in serum calcium releases parathyroid hormone, which then catalyses the conversion of 25(OH)D – either from food or from de-novo synthesis in the skin and liver – to active 1.25(OH)$_2$ in the kidney. This, in turn, increases calcium absorption in the intestine, resulting in an increase in serum calcium and a flattened control loop. Excess calcium that may be produced during this process is stored in the bones. Osteosynthesis is therefore a possible and not an imperative consequence of VitD activation. It only occurs if an excess of calcium is obtained during the activation of the control loop. As both the controlled variable (serum calcium) and the manipulated variable (parathyroid hormone) are systemic, the entire control loop is also referred to as the central, systemic, osseous or musculoskeletal VitD metabolism. While this involves highly PTH-sensitive intestinal and renal tissue, a local or peripheral VitD metabolism exists in parallel.

THE PERIPHERAL VITAMIN D METABOLISM

This dominates in extraintestinal and extrarenal tissue, and includes microglia and neurons, cells of the immune system and adipocytes *[10]* – tissue types that play a key role in chronic inflammation. It acts upon the specific needs of the individual cell on site and therefore on the local environment. In this case, control and regulating variables differ greatly from central regulation. The main issue is the relationship between VitD-activating enzymes and VitD-deactivating enzymes, with the former represented by CYP27B, and the latter by CYP24. Both are mainly found in the mitochondria and, to a limited extent, also in the endoplasmic reticulum. This means that the mitochondrial density and mitochondrial function of a cell, which can deviate significantly from the standard, particularly in chronic inflammatory processes and persistent oxidative environments *[11]*, is a not insignificant factor for functioning VitD regulation. Stimulation of CYP27B1 and consequently the conversion of 25(OH)D into 1.25(OH)$_2$ occurs mainly through proinflammatory signals. These include certain cytokines (IL-1, IL-2, IL-6, TNF-α and IFN-γ) *[12]* or TLR- or NOD-activating microbial stimuli (e.g. LPS or viruses) *[13]*. The background is the induction of AMPs *[14, 15]*, [] (antimicrobial peptides, e.g. defensins) and nitrogen oxides (NO) *[16]* by 1.25(OH)$_2$, which in turn are decisive for the defence against the triggering infectious factors. We can apply the following rule of thumb: The more inflammatory the environment, the more pronounced the conversion of 25(OH)D to 1.25(OH)$_2$.

Note: To indicate vitamin D concentrations, this article uses (mol). When converted to g, this is roughly mol/2.4. As a generic term, vitamin D is abbreviated to VitD. Unless stated otherwise, the designation 25(OH)D comprises the sum of calcidiols 25(OH)D$_2$ and 25(OH)D$_3$. Similarly, the sum of calcidiols 1.25(OH)$_2$D$_2$ and 1.25(OH)$_2$D$_3$ applies for 1.25(OH)$_2$.

Membranary and Intracellular Vitamin D Receptors

BOUND AND UNBOUND VITAMIN D

As a lipophilic metabolite, VitD is mainly found in the body in protein-bound form. For transport in the bloodstream, vitamin D binding protein (VDBP) is available as a specific carrier and, to a much lesser extent, albumin as a non-specific carrier. This applies to both 25(OH)D and $1.25(OH)_2$. Both reach the target cell primarily bound to their carrier. This initially trivial context is of crucial importance, as free $1.25(OH)_2$ either diffuses through the membrane following the local concentration gradient or binds to membrane receptors (MARRS, Membrane-Associated Rapid Response Steroid-binding Receptor). In contrast, VDBP-bound VitD enters the cytoplasm via the megalin transporter and bound to the carrier (Fig. 1).

Unfortunately, current laboratory tests do not allow differentiation into bound and unbound VitD, regardless of whether it is 25(OH)D or $1.25(OH)_2$. If this perspective is taken into account at all, it primarily takes the form of extrapolation by determining the total levels of individual VitD metabolites in the plasma and calculating the bound fraction from the levels of VDBP and albumin *[17]*.

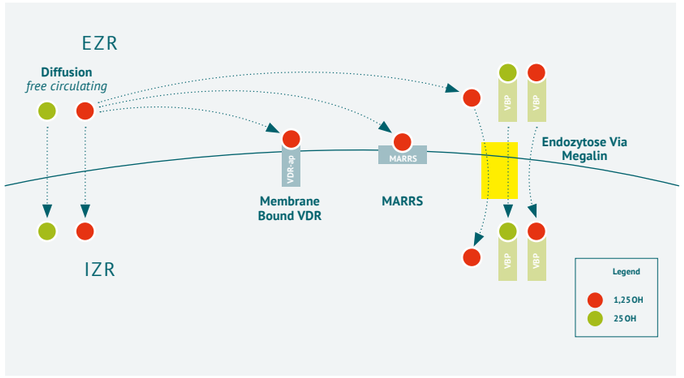


Fig. 1) Transmembrane transport of vitamin D

However, as we will see in the following section, the relationship between bound and unbound VitD is not of inconsiderable significance as to the effects which are triggered in the target cell. In this case it is remarkable that although the levels of binding proteins (VDBP, albumin) regulate the levels of circulating VitD metabolites *[18]*, these have no influence on the formation of binding proteins *[19]*. Albumin production is subject to other regulatory factors and VDBP is constantly synthesised in the liver. Fluctuations in VDBP levels are only found in certain situations and independent of the VitD metabolism, e.g. in the context of oestrogen therapy or nephrotic syndrome *[20]*. Consequently, a high supply of binding proteins lowers the fraction of freely circulating VitD, whereas an increased supply of VitD does not automatically lead to an increase in binding capacity, but to an increase in free VitD. For example, a high-dose VitD therapy or, for reasons yet to be investigated, an increased formation of $1.25(OH)_2$ can result in increased free VitD. This correlation deserves far more attention than it is currently receiving. More important than the question of absolute VitD levels is that of the ratio between 25(OH)D and $1.25(OH)_2$, and between free and bound VitD. As laboratories are unable to perform a direct and comprehensive breakdown of the individual fractions to date, the therapist must use indirect measuring methods to shed some light on this issue. In this the options include the analysis of the VitD ratio, ideally in conjunction with cytokine profiles (cf. section on VDR blockade).

MEMBRANE SIGNAL CASCADE

The membranary, MARRS-supported effect of VitD differs diametrically from the VDR-supported epigenetic-nuclear effect. Among other things, MARRS organises the influx of calcium into the cell and activates osteoclasts (whose VDR expression is physiologically extremely low) *[21]*. Depending on the cell type, the increase in intracellular calcium can lead to increased formation of NFkB and the associated pro-inflammatory cytokines *[22, 23]*. Among other things, it was possible to show that inhibition of MARRS21 or calcium influx inhibits the release of pro-inflammatory cytokines (PIC) *[24]*, whereby MARRS is in competition with the intracellular VDR: It has been shown that malignant cells with MARRS knockout respond more strongly to VitD treatment, with significantly slower cell division rates *[25]*. Also relevant in the context of oncological diseases: MARRS is able to activate tyrosine kinases [26], an important promitotic signal in many malignant cell lines. In general, a decrease in VDR expression is observed during carcinogenesis *[27]*. By means of translocation into the cytoplasm, the MARRS protein interacts with NFkB and can have a proinflammatory, but also a differentiating effect *[28]*. The phenomenon of a dominant MARRS activity at low VDR expression is of crucial importance for our consideration, as it can reverse the effect of VitD. Promitotic instead of antiproliferative, proinflammatory instead of tolerance-promoting, pro-oxidative instead of reductive *[29]* and osteolytic instead of osteoprotective. The following factors are decisive for setting the course of the signal cascade:

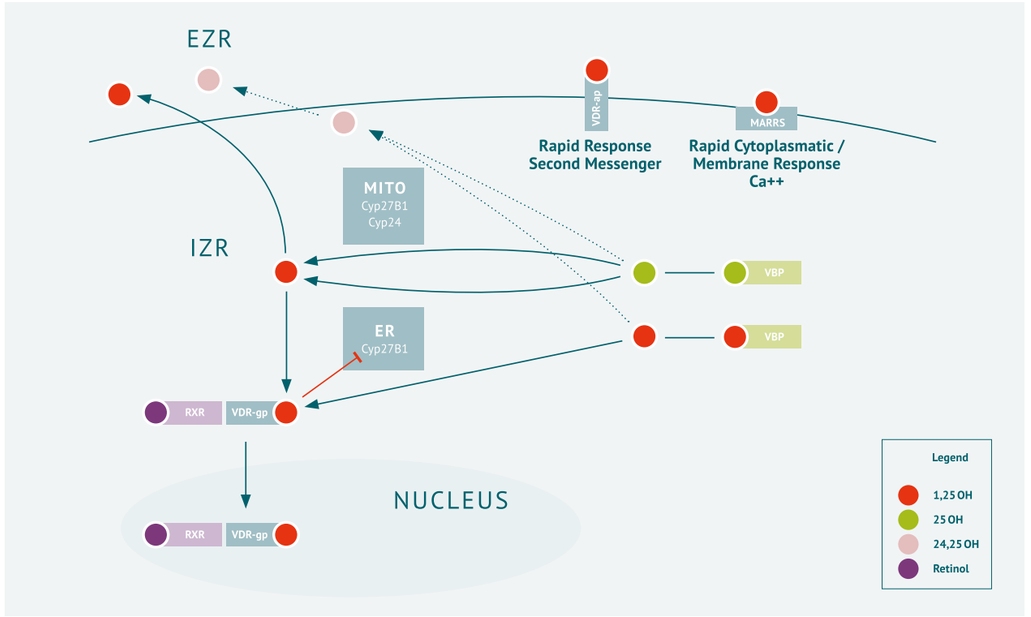


Fig. 2) VDR/RXR as nuclear transcription factors

- the expression and ratio of MARRS to VDR in the target cell
- availability of free $1.25(OH)_2$ at the cell membrane
- and therefore, the ratio of protein-bound VitD to free VitD in the plasma

The lower the VDR expression, the larger the fraction of free VitD and the higher the proportion of $1.25(OH)_2$ in total vitamin D, the earlier and the more pronounced the response of MARRS with membrane effect instead of the VDR with nuclear epigenetic effect.

INTRACELLULAR SIGNAL CASCADE

Physiologically, the majority of VitD bound to VDBP enters the cell, where the CYP27/CYP24 ratio is used to decide on the further path (Fig. 1). Following the appropriate stimuli, $1.25(OH)_2$ is released in the cytoplasm and subsequently bound to the VDR, which is found unsaturated in both the cytoplasm and the cell nucleus. The latter is significant in that the unsaturated VDR already functions as a negative transcription factor by blocking at the DNA target structures (repressor function). To fulfil its role as a positive transcription factor (activator), two conditions must be met. Firstly, the VDR must be saturated with $1.25(OH)_2$. Secondly, and this is often neglected, the VitD-saturated VDR needs a co-activator: RXR. Analogous to the VDR/VitD pairing, this is a receptor for vitamin A in the form of retinol. Sufficient transcriptional control by VitD therefore requires a sufficient availability of retinol to saturate the RXR *[10]* (Fig. 2).

In contrast to MARRS activation, VDR primarily mediates genomic effects, whereas the former develops cytoplasmic effects via a second messenger. In this case it should be noted that the physiological effects ascribed to VitD are based on the genomic signalling pathway via VDR. We recall the example already mentioned: Osteolysis via MARRS versus osteosynthesis via VDR.

Vitamin D and the Immune System

OVERVIEW

It was already emphasised in the introduction that sweeping statements about VitD and the immune system do not reflect reality in any way. In actual fact, the effect of VitD on our immune system is highly differentiated. A detailed discussion on the numerous effects and their interactions would go far beyond the scope of this publication. However, there is a wealth of available further literature. It remains true that an adequate supply of VitD (as defined by the 25(OH)D level) protects against infections *[30]*, and that low VitD levels conversely increase the risk of infection. This has recently been demonstrated again for SARS-CoV2 *[31]*. However, this is merely gross simplification. Reality may differ considerably in individual cases.

It is therefore essential not only to have a rough idea of the overall situation, but also to pay more attention to certain details. The following explanations apply to an intact signal cascade pursuant to the $1.25(OH)_2$/VDBP VDR axis. In general, VitD leads to an increase in activity in the non-specific immune system, while the specific immune system shows an increase in tolerance: Specifically, macrophages/monocytes *[12]* (MC) and natural killer cells (NK) are stimulated, while important representatives of the specific cellular defence are inhibited, including Th1 helper cells *[32]*, Th17 helper cells and dendritic cells (DC). VitD also increases the activity of tolerogenic lymphocytes, such as regulatory T cells (T-Reg) and IL-10-secreting Th2 lymphocytes *[33]*.

In the context of the VDR blockade, which is still to be discussed, we must at least take a closer look at some detailed aspects:

VITAMIN D AND MACROPHAGES

Macrophages, together with neutrophilic granulocyte carriers, represent the primary immune response. Their task is to link the non-specific with the specific defence. This mainly follows by antigen processing and antigen presentation as part of the phagocytosis activity and recruitment of NK which, in turn, is stimulated by VitD. In contrast to DC, the antigen presentation of MC can only reactivate a pre-existing immunity of the lymphocytes (activation of T-memory and plasma cells with subsequent production of antigen-specific CD8 lymphocytes and antibodies), but not induce specialisation in a new antigen. It should also be noted that VitD induces the M2 phenotype within the MC population *[34]*. This polarisation is characterised by a lower production of radicals (ROS), nitrogen oxides (NO) and PIC (including IL-6, TNF-α, IFN-γ) compared to the M1 phenotype, which, in turn, is mainly induced by PIC and TLR-7 agonists such as LPS *[35]*.

VITAMIN D AND AMP

In the event of an infection, the affected cells and, to an even greater extent, activated immune cells are able to express so-called antimicrobial peptides (AMP). These are particularly important in the early phase of an infection to prevent exponential growth of the pathogen, to recruit immune components and to support antigen production *[36]*. In this case AMPs are not only effective against bacteria, but also against a variety of viruses *[37]*.

The main stimulus for the formation of AMP is the stimulation of Toll-like-receptors (TLR) by recognition of microbial components, which initiates the transcription of the AMP-coding genes via the formation of $1.25(OH)_2$ and subsequently via the VDR *[15]*. This is certainly part of the explanation why insufficient VitD levels correlate negatively with the general risk of infection. At this point, it should be noted that sufficient AMP synthesis can only take place under the condition of sufficient

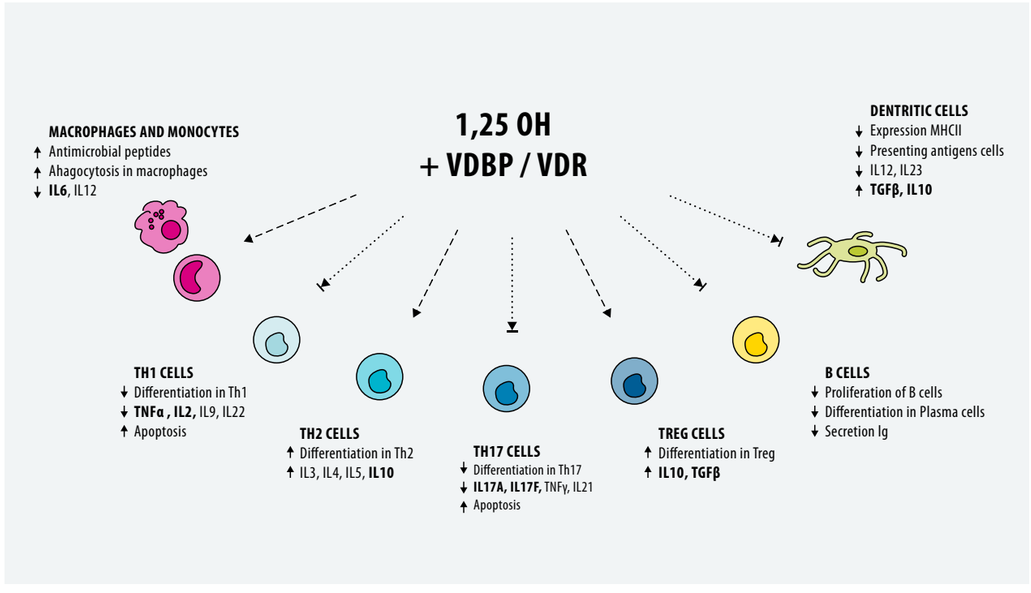


Fig. 3) The effect of vitamin D on specific and non-specific defence

translocation of $1.25(OH)_2$-saturated VDR into the cell nucleus. Inadequate levels of $1.25(OH)_2$, VDR, RXR and/or retinol automatically lead to limited AMP formation.

VITAMIN D AND NF-иB

The transcription factor NF-иB (nuclear factor kappa B) plays a key role in the formation of cytokines, chemokines and metabolic modulators in response to an infection *[38]*. Apart from the activation of TLR and NOD, PIC such as TNF, IL-1, IL-2, IL-6 stimulate the formation of v, which in turn massively increases their release. The NF-иB signalling pathway is one of the most powerful proinflammatory signalling pathways of all. It is therefore of enormous importance to subject this cascade to strict regulation. Dysregulation poses a risk of sustained and/or excessive inflammatory reactions. Astonishingly, it is here of all places that an amazing vulnerability becomes apparent. Both the inhibition of NF-иB activation by TLR and the inhibition of NF-иB activity by negative feedback follow via SOCS1 (suppressor of cytokine signalling 1). However, this is now inhibited by NF-иB itself. In other words: NF-иB inhibits its own inhibition. The possible consequence: disinhibited NF-иB activity. The crucial factor for the successful modulation by SOCS1 is NF-иB O-induced suppression of SOCS1 inhibition by $1.25(OH)_2$/VDR *[39]*. This is the only way to ensure adequately controlled PIC release (Fig. 4).

If the VitD-VDR axis is compromised, there is not only a general risk of uncontrolled release of proinflammatory signals, but also the potentiation of this effect by insufficient AMP expression. This would result in the prolonged and increased release of PIC, with extremely negative consequences in the short, medium and long term. The risks for acute hyperinflammation (cf. cytokine storm in Covid-19), chronic and silent inflammation as well as autoimmunity would increase significantly. The phenomenon of anamnestically encountering certain infections, which then mark the beginning of a chronic inflammatory disease, is well known in practice. In particular, certain intracellular pathogens are found here disproportionately often (EBV, CMV, Borrelia, etc.). Epidemiologically, an insufficient VitD supply is known to correlate with an increased risk of autoimmune diseases *[40]*. The explanations given so far already permit first conclusions as to why this is so. Tolerance reduction in the specific immune system, increased risk of infection and increased readiness for hyperinflammation form a skilfully unfavourable conflict situation. So far, we have assumed an intact VDR signal cascade. But what if this does not exist?

TheVDR Blockade: The Perfect Storm

A »Perfect Storm« refers to the emergence of an exceptionally unfavourable situation from the combination of several factors that are unfavourable in themselves. This is the case with the VDR blockade. Or, to use the immortal words of Jürgen Wegmann:

»First we were unlucky and then we had bad luck as well«.

THE CONCEPT

From the author`s perspective, the concept of a blockade is somewhat unfortunate, as it all too easily evokes a mental association of the VDR being physically blocked by binding metabolites of whatever kind. So far, this could only be shown in computer models *[41]*, but not confirmed in vivo. According to current research, what is more important is the reduced availability of the VDR protein as a result of its reduced expression. In other words, what is actually blocked is the VitD-VDR signalling path. In this sense, we have already become familiar with two variants of the VDR blockade: Firstly, the shift of the $1.25(OH)_2$ effect away from a genomic VDR-supported to a membrane-supported MARRS. The background here was the increased occurrence of free $1.25(OH)_2$ due to disproportionate VD metabolites to their binding proteins, in particular the VDBP. Secondly, the lack of saturation of the VDR cofactor RXR with retinol. We will now turn to the direct expression-modulating factors.

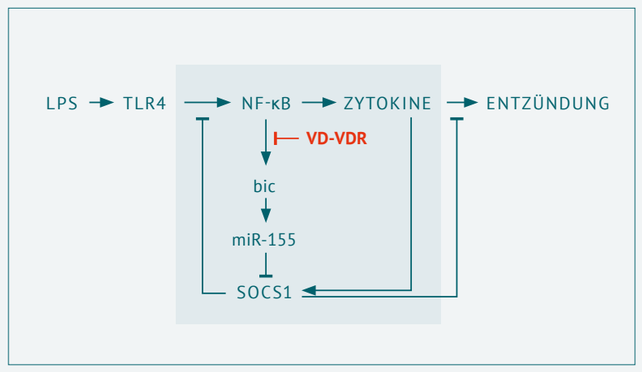


Fig. 4) Vitamin D controls NF-иB activity; according to Chen, 2013

THE VITAMIN D RATIO

The generally recognised epidemiological truism that low VitD levels are associated with increased risk of disease for a wide range of chronic conditions has been pointed out several times. However, more detailed studies have revealed interesting observations in this respect. Chung et al 2011 have shown that, although low 25(OH)D levels increase the risk of developing various diseases, therapeutic elevation of 25(OH)D levels does not yield significant clinical benefit when the disease occurs *[42]*. A widely acclaimed 2014 review published in Lancet came to a similar conclusion. Autier et al *[43]* concluded that low 25(OH)D levels correlate with the increased occurrence of chronic inflammatory processes, but conversely, the forced administration of 25(OH)D had no positive effect on those affected. Similar findings also exist for cardiovascular diseases *[44]*. A lack of VitD is therefore obviously a problem, but VitD administration is not necessarily a solution – at least not when the pathophysiology has developed to a clinical level. Finally, a breakthrough came with the observation that patients with clinical manifestations, especially those with chronic inflammatory and autoimmune pathologies, not only had the expected low 25(OH)D values, but also elevated $1.25(OH)_2$. A very strong positive correlation between traditional inflammation markers such as CK and CRP with the level of $1.25(OH)_2$ was also found *[45]*. Simply put: The more calcitriol measured, the more inflamed the patient. Blaney et al were able to show that in autoimmune patients and patients with CFS, increased calcitriol was much more prevalent than decreased calcidiol (Fig. 5).

Since hypercalcaemia was not detectable in any of the investigated cases, despite elevated $1.25(OH)_2$, the authors postulated an insufficient signal transduction via VDR. The positive effect of an increase in VDR expression, or the negative impact of VDR deficiency on autoimmune diseases, is well documented. It could be shown that VitD only protects effectively against autoimmune diseases in the presence of sufficient VDR *[47]*. This gave birth to the idea of a VDR blockade and brought VDR availability and its expression into the focus of interest. In this case, the Australian scientist Trevor Marshall had already gained decisive insights a few years earlier in remarkable but long neglected pioneering work. His initial observation that certain angiotensin receptor blockers had astonishing immunomodulatory effects in addition to their actual action *[48]* finally led him to a much more comprehensive insight. While many pathogens are able to suppress essential parts of the immune response by reducing VDR expression and can therefore trigger a persistent, chronic infection, it is precisely these infections that are successfully combated by interventional restitution of VDR expression *[49]*. The resulting Marshall Protocol for the treatment of autoimmune diseases and chronic infections is essentially based on three components: Firstly, the reduction of intracellular pathogens through antibiotics (minocycline, clindamycin, bactrim and declomycin are recommended, depending on the initial situation) to reduce VDR repression. Secondly, the angiotensin receptor antagonist olmesartan to increase VDR expression. Thirdly, and equally importantly, avoiding the intake of 25(OH)D. At first sight, this requires some explanation, as the low level of 25(OH)D is generally considered to be the main problem. However, the fact is that, with a given VDR deficiency, the affected cell reacts by upregulating the 25(OH)D conversion to $1.25(OH)_2$. The result is a veritable $1.25(OH)_2$ excess which, in turn, inhibits the expression of VDR *[50]*. In the context of a chronic infection, it can also be assumed that PIC increases the activity of CYP27B1, meaning that basally increased $1.25(OH)_2$ formation is already present, aggravated by the problems already described with regard to LMP and NF-иB . It is therefore imperative

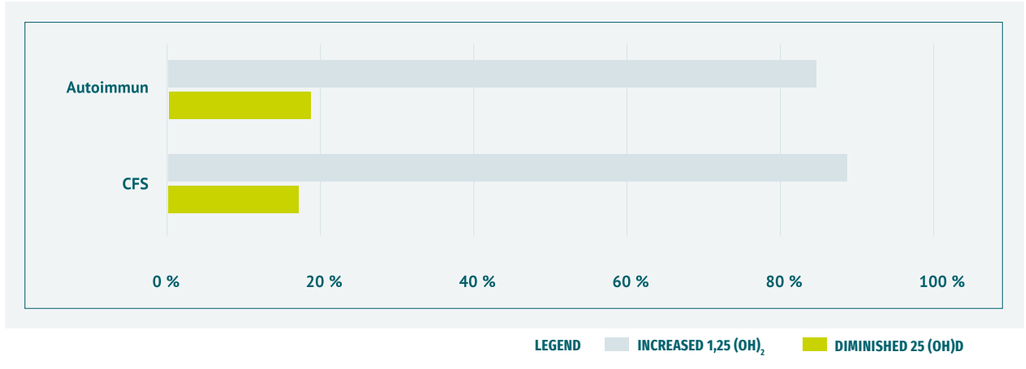


Fig. 5) $1.25(OH)_2$ surplus and 25(OH)D deficiency as health markers

to parameterise the VitD status of the patient in more detail. In addition to the determination of the 25(OH)D level, $1.25(OH)_2$ must be tested and both must be put into a ratio. This is the only way to identify the excessive and ultimately immunocompromising and pro-inflammatory formation of $1.25(OH)_2$, whereby the quotient $1.25(OH)_2$/25(OH)D should ideally be <1. Any increase in the ratio above this value correlates positively with the problems mentioned and may indicate a VDR blockage, be it against the background of increased MARRS activation (keyword: free $1.25(OH)_2$), retinol deficiency (RXR) or VDR expression reduction. The measurement of 25(OH)D alone is not meaningful at best, all the more so as another factor must be taken into account at this point: the problem of reference ranges, which often do not take into account the VDR blockade phenomenon. In concrete terms, the limit values of $1.25(OH)_2$) in particular are clearly too high, in some cases >200 pmol/l. In fact, $1.25(OH)_2$) already correlates with inflammation markers such as CK and CRP from 110 pmol/l *[45]*. In total, this results in the following reference ranges for the individual parameters (Fig. 6).

DIRECT MODULATION OF VDR EXPRESSION

VDR expression is modulated by a variety of factors, both physiologically and pathophysiologically. There is still an enormous need for research to obtain a more comprehensive picture. For example, the question as to which medication and active ingredients lead to increased or decreased VDR expression is likely to lead to a reassessment of the risk-benefit ratio in quite a few cases. Here are just a few known, clinically relevant factors. VDR expression is inhibited by numerous, highly prevalent pathogens (e.g. EBV *[51]*, Borrelia and CMV *[52]*, mycobacteria *[53]* or Aspergillus *[54]*). An impaired composition of the commensal microbiome is also of enormous importance in terms of bacterial translocation and production of epigenetically modulating miRNA *[50]*. In principle, it can be assumed that all intracellular pathogens use the inhibition of AMP synthesis via reduced VDR expression as an essential survival strategy to a greater or lesser extent. The body›s own signals can also contribute to this problem both directly (classic: TNF-α *[55]*) and indirectly (excessive $1.25(OH)_2$ formation, cf. PIC and CYP27B1). In particular when increased conversion of 25(OH)D to $1.25(OH)_2$ is observed (increased VitD ratio, especially with high to elevated $1.25(OH)_2$ values at normal to low 25(OH)D values), the administration of VitD is contraindicated. This would further extend the problem of reduced VDR expression induced by the excess $1.25(OH)_2$. Under these conditions, vitamin D would have a proinflammatory and immunocompromising effect (AMP formation!). Chronic inflammatory pathologies and any existing infections, especially intracellular infections, would ultimately be encouraged. Against this background alone, it is imperative to check the VitD ratio prior to each VitD substitution.

In addition to Olmesartan mentioned above, several other metabolites have a beneficial effect on expression, most notably butyrate, an SFCA formed by our microbiome *[56]*. While dysbiosis with reduced butyrate formation is a problem for the VDR axis, prebiotic intervention with SCFA precursors can be an important part of the solution in individual cases.

	$1.25(OH)_2$	25(OH)D
Mol	48 – 110 pmol/l	50 – 120 nmol/l
g	20-46 pg/l	21-50 ng/l
VD-Ratio	< 1	

Fig. 6) Adjusted reference ranges with consideration of the VDR blockade

INDIRECT MODULATION OF VDR EXPRESSION

Indirect approaches are also suitable for normalising VDR expression. In this case the consideration is to eliminate barriers to expression, with intervention possibilities existing at several levels. For example, we can test for factors that contribute to an overactivation of CYP27B1 and therefore to excess $1.25(OH)_2$. In case of a positive result, their neutralisation would be an important part of treatment:

- Nitrosative stress (NO and ONOO) - proven antidotes are methylcobalamin and curcumin
- LPS (traditionally: Leaky Gut) - fast reduction, e.g. with Salutosil®
- PIC – in this case, suitable active substances can be identified by means of TNF-α inhibition tests, traditionally with polyphenols, for example
- Insufficient calcium supply (leads to the release of parathyroid hormone, which in turn massively stimulates CYP27B1) – solution is the administration of calcium (together with magnesium and vitamin K2)

The problem of excess $1.25(OH)_2$ can also be addressed by providing exogenous VDBP (e.g. BIC Immun®). In an excellent study, Kongsbak 2014 was able to show that VDBP inhibits the excessive formation of $1.25(OH)_2$ as well as the release of PIC *[57]*. The binding of free $1.25(OH)_2$ can also counteract an increased response of the MARRS. This is of great importance because the MARRS-induced increase of calcium in the cell not only has a proinflammatory effect but also inhibits VDR expression *[58]*.

THE BODI PROTOCOL

Based on the observation that the administration of VDBP, especially in patients with inflammatory indications and CFS, leads to a significant improvement not only of the laboratory parameters but also of the clinical situation, the Munich physician Christian Burghardt developed a protocol for the comprehensive treatment of VDR blockade. Named the BODI Protocol after the institution he heads, it tries to take into account as many of the factors explained above as possible.

The main component is VDBP, whose tasks are to bind free, excessive $1.25(OH)_2$, associated with the shift of action from MARRS to VDR, and to reduce intracellular hypercalcaemia. As a second component, a mineral mix of Ca, Mg and boron covers systemic regulation via PTH. Adequate extracellular calcium supply prevents sustained PTH activity, therefore decreasing the conversion of 25(OH) D to $1.25(OH)_2$. The lipophilic vitamins A, D, E and K are also used. Vitamin A (in already bioavailable form) ensures saturation of the co-receptor RXR, vitamin E counteracts oxidative and nitrosative stimuli, and vitamin K2 supports calcium homeostasis. Vitamin D is kept very low (<2,000 IU/d) so as not to promote any increased VitD conversion that may still exist. Finally, the protocol includes the use of a phytotherapeutic complex mixture of bacteriostatic and virustatic properties. Their task is to take over the function of antibiotics in the Marshall Protocol, i.e. eliminating any existing intracellular pathogens. The advantages over the Marshall Protocol are obvious:

- Microbiome-contaminating and potentially mitochondria-toxic antibiotics are avoided.
- Central dysregulation by PTH in the context of impaired Ca-homeostasis is covered.
- Important modulators such as RXR/ vitamin A, MARRS and the inhibition of NF-ʁB are considered.
- With VDBP, the main effect is based on a body-analogue protein from natural sources.

Synthesis

DIAGNOSTIC SUMMARY

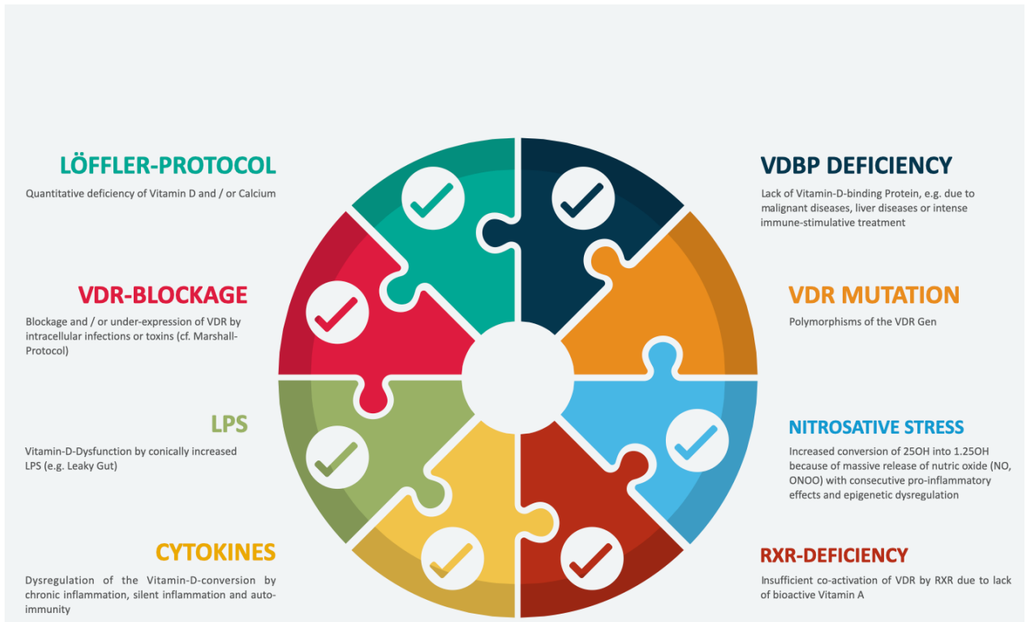
A compelling conclusion from this consideration of the VitD metabolism must be that a sufficient diagnosis goes far beyond the measurement of 25(OH) D. The minimum requirement is the VD ratio and, in this case, the laboratory independent limitation of $1.25(OH)_2$ to <110 nmol/l. The Ca level can also be determined. Elevated calcitriol with simultaneous normal or low calcium can only be explained by a VDR blockade. These simple measurements at least reliably indicate potential problems in terms of VDR blockade – but not the pathophysiological and aetiological background. A broader approach is needed to gain information here: cytokine profiles, nitrostress profiles, NK activity, testing for LPS, intestinal permeability markers and a microbiome status. It should also be noted that a culture test is clearly not enough; the metagenome and metabolome (butyrate!) must be tested instead. In the future, proteomic and mRNA expression profiles using NGS (Next Generation Sequencing) will provide even deeper insights. For the moment, however, this is still limited to research.

TREATMENT OUTLOOK

No matter which treatment protocol is chosen following the identification of a VDR blockade (Marshall, BODI), it must be clear that, in the vast majority of cases, the strategy cannot be to administer higher doses of VitD. Following the cytokine profiles of patients, daily doses of >5,000 IU often turn out to be problematic. Not in the sense of acute complications – the frequently invoked hypercalcaemic crises simply do not occur due to the absence of VDR signal transduction – but in the sense that a VDR blockade is consolidated or even extended. High-dose VitD therapy (with single doses of 50-300x10^3 IU/d) with intact VDR function must be distinguished in this case. Here, for example, the tolerogenic effect of VitD on the specific immune system can be developed into an immunosuppressive effect, with a very well-known example being the treatment of MS exacerbation.

IN THE CONTEXT OF CORONA

In this regard, it is important to distinguish between prophylaxis and intervention in case of illness. As a preventive measure, care should be taken to ensure that there is no VDR blockade but a physiological distribution of the VitD parameters (cf. Diagnostic summary). Higher doses of VitD (>5,000 IU/d) without knowledge of the VitD ratio are not recommended, as the worst-case scenario may be an unproductive, pro-inflammatory effect. With an impaired VDR function, a latently increased level of inflammation in the organism can generally be assumed. In particular, TNF-α, IL-6 and IL-17 should not be elevated, as this could promote a hyperinflammatory course of Covid-19. VDR blockade would also promote rapid exponential proliferation of SARS-CoV2 through impaired AMP formation, which tends to be more complicated and severe. In turn, VitD deficiency leads (via insufficient activity of macrophages and NK cells) to significant deficits in the primary immune response, especially with regard to the formation of virustatic IFN-γ. High doses of VitD can be considered to combat hyperinflammatory tendencies that have already occurred, but only if VDR blockade has previously been ruled out.



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