

Fact sheet Vitamin D, Sun and Multiple Sclerosis (Update 2019)

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Background

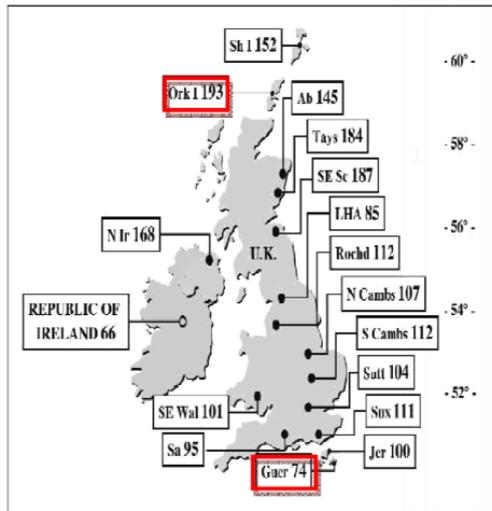


Fig. 1 Distribution of MS in the UK and the Republic of Ireland. Study area (prevalence year): *Sh I*, Shetland Islands (1974); *Ork I*, Orkney Islands (1983); *Ab*, Aberdeen (1980); *Tays*, Tayside (1996); *SE Sc*, South East Scotland (1995); *LHA*, Leeds Health Authority (1996); *Rochd*, Rochdale (1989); *N Cambs*, North Cambridgeshire (1993); *S Cambs*, South Cambridgeshire (1990); *Sutt*, Sutton (1985); *Sux*, Sussex (1990); *Jer*, Jersey (1991); *Guer*, Guernsey (1991); *Sa*, Southampton (1987); *SE Wal*, South East Wales (1985); *N Ir*, Northern Ireland (1996); Republic of Ireland (1971)

Many previous observational studies have shown that the frequency of MS has a clear north-south gradient. In addition, there was fewer incidence of MS in coastal regions compared to the inland. Furthermore, MS prevalence may change after migrations that occurred during the second decade of life, with a beneficial effect for people who migrated from a high-latitude region (with a high MS prevalence) to a sunnier, lower-latitude region, with a low MS prevalence. It became evident from these observation that MS-frequency depends on latitude (and thus the annual solar radiation dose in the region concerned), besides regional

eating habits and genetic predisposition. The relationship between sun exposure and MS prevalence becomes even more apparent when examining genetically nearly homogeneous regions with similar diets. The figure above shows the north-south gradient of MS prevalence in the United Kingdom. Up into the nineties, the difference between the Guernsey Region and the Orkney Islands was a factor of 2.5 in the number of cases per 100,000 population over only 8 degrees of latitude north-south difference (Rosati 2001).

However, this pronounced geographically oriented epidemiological aspect in the development of MS cannot be upheld like this any longer. This is because of increasing lifestyle changes occurring parallel to the growing industrialization, independently of latitude. The comparison of two studies involving white nurses in the United States clearly demonstrates this. The first study, which was carried out at the beginning of the last century, showed that participants from the Northern states were approximately three times more likely to suffer from MS than participants from Southern states. In the second study, which was conducted in the second half of the last century, no significant difference was found in the incidence of multiple sclerosis between the Northern and Southern states in this population (Ascherio 2013).

Even more impressive are findings from Iran, whose capital Tehran lays approximately on the 36° latitude. Its geographic location corresponds to the Southern Mediterranean countries and the Southern United States which are quite sunny regions. Alongside economic and political changes in recent decades, a dramatic increase in MS incidences was reported. In Tehran, for example, the disease incidence (Elhami 2011) increased in women by a factor of eight in less than 20 years. Similar trends were also observed in the rest of Iran, especially in big cities. Parallel to this, a widespread and pronounced vitamin D deficiency was detected in the country, particularly amongst women (due to use of covering clothes). Clearly, lifestyle factors have become more crucial than latitude in determining MS prevalence (Etemadifar 2013). This is highly relevant for considerations in the primary and secondary prevention of multiple sclerosis.

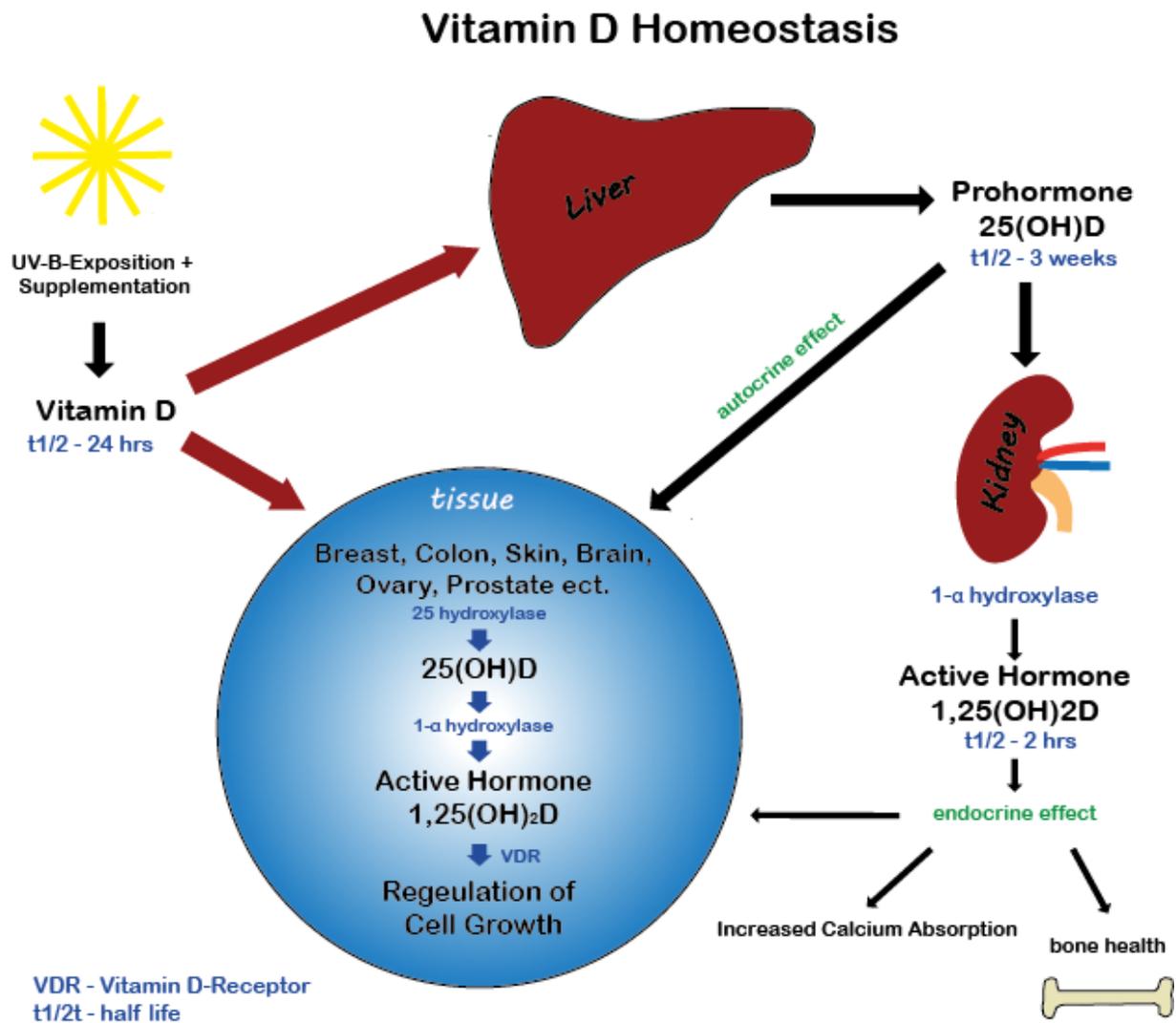


Figure 2. Schematic representation of the vitamin D metabolism.

Numerous studies confirm the association between lack of sunlight, vitamin D deficiency and risk of MS (Pierrot-S et al., 2018). This becomes understandable when looking at the dependence on the physical process on the skin to the formation of vitamin D in the body (Figure 2). For this purpose, UVB rays of certain intensity must penetrate the surface of the skin at a certain angle. In latitudes geographically north of 40 degrees, sunlight is enough for proper formation of vitamin D only in the period from April to September at noon.

What does lack of sunlight mean?

Most importantly, it means that the production of vitamin D through UVB radiation on the skin does not occur. Only a small part is obtained by food. Vitamin D is a pro-hormone, which is needed not only for bone metabolism but also for healthy functioning of literally all organs. Furthermore, up to 1000 genes are triggered by vitamin D. For example in Germany, a vast majority of the population irrespective of age suffer from vitamin D deficiency. This is true particularly in the winter months as demonstrated in a study involving 5000 patients from the Rhine-Main area (Lemberg 2012). Only infants supplemented with vitamin D had normal levels (over 30 ng/ml). The wide impact of vitamin D on the healthy functioning of our bodies is best documented for the skeletal system but it also plays a role in almost all chronic diseases, from cardiovascular system disease to cancer and almost always involving the immune system. The latter is discussed further down in more details.

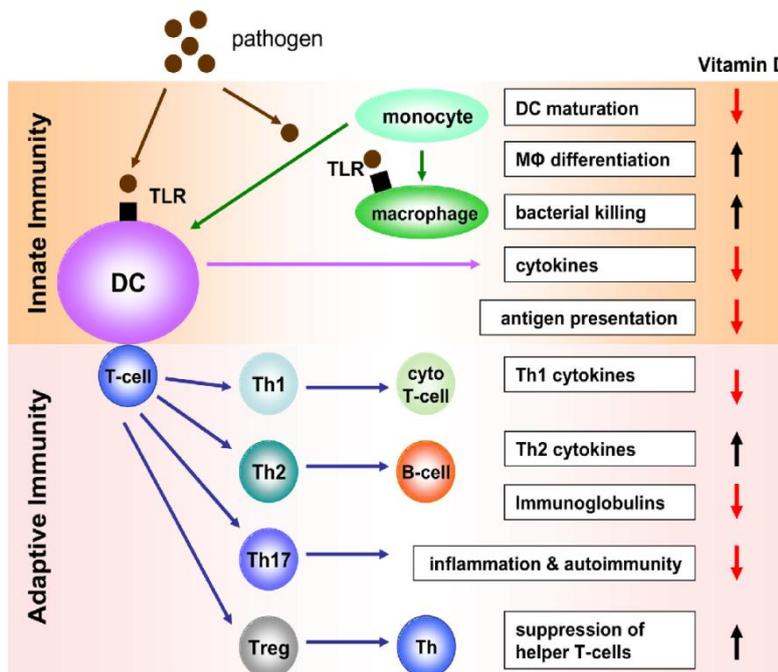


You will find detailed information on the overall health consequences of a vitamin D deficiency on the SonnenAllianz website:

www.sonnenallianz.de

Vitamin D deficiency as a risk factor for MS is therefore mainly an environmental problem due to lack of sunlight. As numerous genetic studies have shown today, there are also disorders in vitamin D metabolism (polymorphisms of enzymes or receptors), i.e. vitamin D metabolic disorders (Pierrot 2017).

Vitamin D and the immune system



A great number of findings were published showing that vitamin D plays an important role in the pathophysiology of autoimmune diseases. This observation was particularly supported by experimental studies demonstrating that vitamin D is instrumental in regulating the production of chemokines, counteracting inflammation in autoimmune diseases and facilitating the differentiation of immune cells so that tolerance to its own tissue is increased. Chemokines are a group of signaling proteins which regulate the attraction of immune cells to the site of inflammation

(see figure 3, Hewison 2010). The risk of severe or very severe vitamin D deficiency is particularly high in patients with MS. A Dutch study involving a few hundred MS patients (Smolders 2008) reported an average vitamin D blood level of just below 20 ng/ml and clearly showed that degree of disability (EDSS) was closely correlated to vitamin D status.

The greatest effect of vitamin D in MS is therefore immune modulation as described above. In addition, neuroprotective and growth-promoting influences on the central nervous system have been demonstrated (Pierrot 2017).

Consequences for the treatment of MS: modulation of disease activity

Several studies from Europe (Marrie et al. Neurology 2017) show the causal relationship between a low 25 (OH) D level and the risk of developing multiple sclerosis.

The authors of the above-mentioned study draw the following conclusions for the treatment and prevention of multiple sclerosis: **“the intake of vitamin D up to very high doses is harmless even during pregnancy and cost-effective. Thus, the course and the probability of developing MS can be positively influenced with little effort, especially for risk groups (smokers, obese patients).”**



Various association studies have been published in recent years on the subject of vitamin D deficiency. Already in 2010 it was shown that the probability of a relapse decreased by 12 % when vitamin D level in serum was increased by 10 nmol/l (Simpson 2010). Further it has been shown by MRI examination of MS patients that vitamin D deficiency is associated with increased number of Gadolinium uptaking lesions compared to vitamin D levels in the normal range. From which it was concluded that vitamin D has an anti-inflammatory effect in MS.

In addition, 5 comparable studies were conducted in 5 different countries with methodologically similar structures, which correlated vitamin D levels with the likelihood of relapse. Analog statistical models showed the reduction of relapses (MS relapse) in 50 % to 70 % (depending on the study) with an increase of the 25-OH-D level in the blood of 20 ng/ml (figure 4). What is remarkable about these studies is that they were similarly structured (cohort studies of similar size and duration), worked with the same statistical models, on 3 different continents with different climates with adolescents and adults with acute inflammatory forms of MS, with or without basic therapy and with or without vitamin D supplementation. The fact that such different contexts produce a virtually identical picture shows very well the "vitamin D effect" (Pierrot 2017).

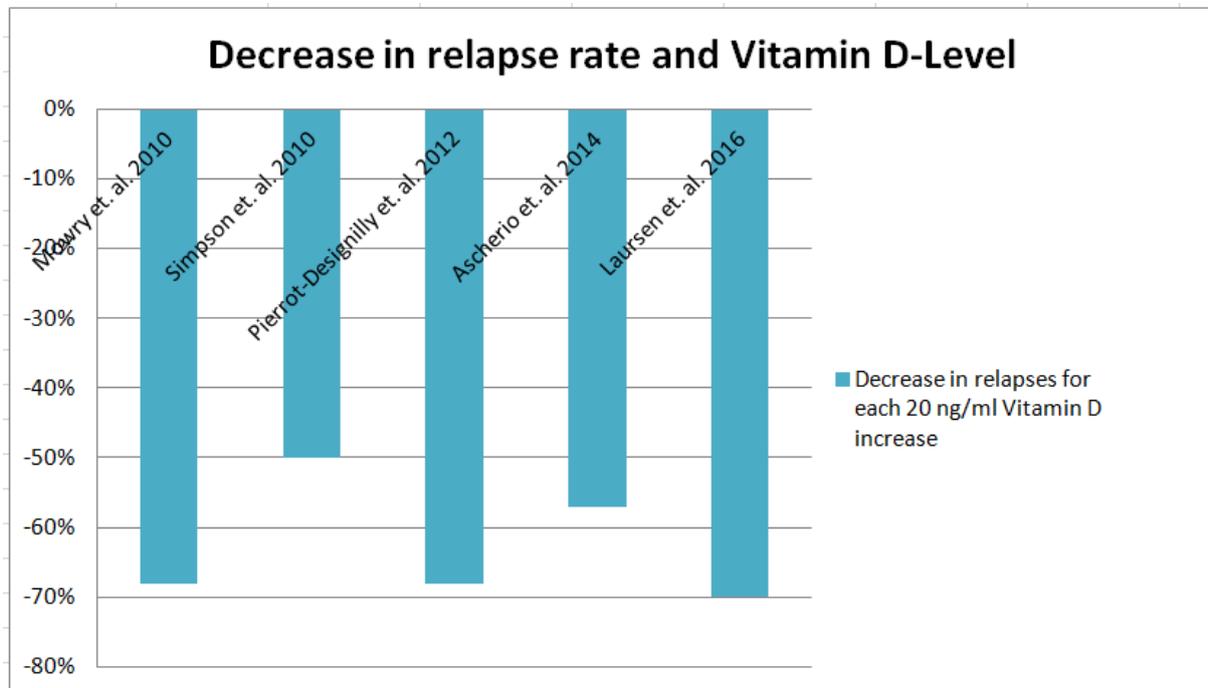


Fig. 4: Overview of comparative studies after Pierrot e.t al. 2017: Reduction of relapse rate and vitamin D level

The effect shown above in studies on the reduction of relapse rates (Pierrot 2017) refers to a certain vitamin D serum level. The effect reaches a plateau in areas above the upper limit of 44 ng/ml (110 nmol/l), i.e. there is no further reduction of relapses. The relapse reduction starts with vitamin D serum values of 30 ng/ml (75 nmol/l) (Pierrot 2017).

Furthermore a recent study with MS patients from Germany (Miclea A. 2017) showed a compensation of seasonal vitamin D deficits and at the same time a modulation of the seasonal occurrence of relapses through supplementation of Vitamin D. These data prove reduced inflammatory activities, especially in the late winter months and in spring, through the administration of vitamin D.

Surely not all about the role of vitamin D in MS is yet known. Still, it is evident that attention to vitamin D level in the treatment of MS is crucial. There are unused opportunities and unnecessary risks taken if the



measurement and optimization of vitamin D in MS treatment is not given priority (Pierrot-D. 2013; Marrie Neurology 2017). Furthermore it needs to be kept in mind that the influence of vitamin D on our bodies goes beyond MS. Vitamin D deficiency is associated with health problems comorbidities with MS such as high blood pressure, depression, metabolism disorders and migraine (Horton, 2010).

High dose vitamin D treatment (Coimbra protocol)

The discussion on the MS treatment approach of the Brazilian neurologist Dr. Cicero Coimbra is currently making waves in the relevant forums and associated comments, especially with regard to multiple sclerosis. The opinion varies somewhere between charlatan, genial spirit and saviour.

Reason enough to reduce the whole thing to the medical content and background in order to be able to better assess the opportunities and risks.

Basic idea

Coimbra assumes that patients with autoimmune diseases have a genetically inherited resistance to the effects of vitamin D. This resistance (including a vitamin D receptor disorder) to the immunomodulatory effect of vitamin D is a partial resistance, not a complete resistance. Due to this predisposition, there is an increased probability of developing an autoimmune disease such as multiple sclerosis. There is preliminary evidence that such gene polymorphisms and vitamin D receptor disorders are more common in MS patients than in healthy individuals (Abdollahzadeh 2016).

The extent of this resistance is determined by measuring parathyroid hormone (PTH) in Coimbra's treatment approach. Vitamin D lowers the level of parathyroid hormone. The response of parathyroid hormone levels to the administration of vitamin D is therefore a measure of vitamin D resistance. Accordingly, the specific dose of vitamin D for each patient is determined by the reaction of the parathyroid hormone level. However, daily doses are used which, according to today's understanding, can be toxic. The oral doses range from 30,000 to 300,000 I.U. vitamin D per day.

History of high vitamin D doses

Intense sunlight produces in the skin per day up to 25,000 I.U. vitamin D. A daily dosage of this kind seems therefore still justifiable in the form of supplementation.

The amounts of vitamin D produced in the skin are thus much lower than the doses of vitamin D used in the 1930s and 1940s to treat asthma (60,000 to 300,000 I.U.), rheumatoid arthritis (200,000 to 600,000 I.U.) and tuberculosis (100,000 to 150,000 I.U.), which were often associated with the development of toxicity. It was found that many patients began to develop clinically significant hypercalcemia¹ after prolonged administration of vitamin D at these high doses, resulting in several deaths.

Since practical methods for measuring the various forms of vitamin D in the blood were not developed until the 1970s, blood levels of vitamin D associated with this toxicity were never determined in the 1930s and 1940s.

Because of these undesirable side effects, the use of vitamin D for the treatment of the above-mentioned diseases with such high doses fell out of the focus of medicine and was replaced by much lower doses in the range of 400 I.U. known not to cause hypercalcemia or other toxicity, but not clinically effective in the

¹ At first nausea and vomiting, diarrhoea or constipation will appear. Finally, cardiac arrhythmia, listlessness and general muscle weakness occur. If the increased calcium level persists, excessive urination with internal dehydration, psychosis and finally coma occur.



treatment of asthma, RA or TB. However, the small amount of vitamin D equivalent to a teaspoon of cod liver oil was safe in the treatment of rickets.

With the medical and laboratory methods available today, however, the resumption of the approaches described above seems long overdue. Recent studies have shown that even high vitamin D doses between 10,000 and 60,000 I.U./day with regular laboratory control of calcium and parathyroid hormone levels did not trigger hypercalcemia or other negative effects (McCullough 2016). In addition, there were clear indications in tolerability studies of positive immunomodulatory properties of very high vitamin D doses. A reduction of the relapse rate was found to be a side effect, so to speak. During the observation period, the patients with vitamin D supplementation had almost 60 % fewer relapses than the placebo group (Burton 2010). In this sense, Dr. Coimbra deserves the utmost respect for this topic.

Opportunities and risks

"In about 95 % of patients with MS, the disease remains in permanent remission under our protocol. While patients receive the high dose of vitamin D, the disease remains inactive without any signs of new lesions – neither clinical nor laboratory", Dr. Coimbra said in a recent interview.

This percentage seems extremely high and doubtful. It is therefore absolutely essential that the Coimbra protocol is further investigated and validated using scientific methods.

More importantly, patients should not start taking high doses of vitamin D above 10,000 I.U. per day on their own, without medical or laboratory support. The experiment can end fatally, as the protocol used not only includes the dosage of vitamin D, but also, among other things, dietary requirements that must be strictly adhered to!

Those affected who want to start with the Coimbra protocol should therefore look for a doctor who will accompany them intensively and competently. A list of doctors trained by Coimbra can be found here:

<http://coimbraprotokoll.de/protokollaerzte/>

The sun is more than Vitamin D-Production

Recent studies suggest that there may be beneficial effects of sun exposure on immunological system, also through non-vitamin D pathways. One study (Zivadinov 2013) with MS patients showed that summer sun exposure was associated with increased gray matter volume and whole brain volume in MRI of MS patients, independently of 25[OH] vitamin D status.

The non-vitamin D (or partly independent) pathway is as yet much less well known. UV-radiation causes local immunosuppression, resulting in less hypersensitivity reaction. It can also stimulate skin-derived tolerogenic dendritic cells, producing IL-10 (a favorable cytokine), resulting in stimulation of local regulatory T- cells (TREGs) and also TREGs located in lymph nodes. TREGs finally join, via bloodstream, the general immune system, in which they could also have a beneficial action (Pierrot 2017). In addition, it helps to limit melatonin secretion, which can modulate T cell proliferation and activity (Hart 2011). Other UV-radiation induced mediators (cis-urocanic acid and oxidation products of DNA, lipids and proteins) may also contribute to the consequent systemic immunomodulation (Zivadinov 2013). Urocanic acid is formed under the influence of UV-radiation from histidine (non-essential amino acid) in the epidermis and has a direct influence on the formation of T cells and protective immunomodulatory properties (Correale 2013).



It is also worth mentioning the sun role in triggering the formation of serotonin (also called happiness hormone) in the brain. Serotonin not only plays an important part in depression, but also stimulates the formation of new nerve cells.

Important remark with respect to Vitamin D supplementation studies: Any positive non-vitamin D pathway effects of sun exposure will not be apparent in vitamin D supplementation trials and may explain the occasional discrepancies between observational studies and clinical trials (Hartley 2015).

Concrete recommendations

For MS patients, the vitamin D serum levels should be at least between 60 and 90 ng/ml. The upper limit is based on the fact that Vitamin D values up to 90 ng/ml are normal in sunny countries. As the prevalence of MS in these countries is low, it is understandable to orientate oneself towards this upper limit (Alshahrani 2013). Besides, no side effects are observed even when serum levels of vitamin D are as high as 300 ng/ml (Kimball 2017). The side effects, when present, are related to hypercalcemia (calcium above 2,6 mmol/l) and this is the reason why periodic measurements of blood levels of calcium, vitamin D and parathormone (PTH) should be done routinely.

Low levels can be increased through supplementation or monitored exposure to the sun. Regular exposure for about 10-15 minutes a day on as much unprotected skin as possible (at least arms and legs²) is recommended to facilitate the above mentioned physiological effects. A Dutch study showed that depression in MS is inversely correlated with the duration of exposure to the sun whereas Vitamin D supplementation has hardly any influence (Knippenberg 2013). As a maintenance dose 4,000-5,000 I.U. daily (at least in the winter months) is established as a rule of thumb for 70 kg body weight. A regular check of vitamin D (60 - 90 ng/ml), calcium (2,0 - 2,6 mmol/l or 8,5 - 10,0 mg/dl) and parathormone levels is strongly recommended.

Special Note – interferon- β , Tysabri and vitamin D

An important study, particularly for practitioners treating people with MS, showed that administering interferon- β to MS patients with an evident vitamin D deficiency can have disastrous consequences for the patient, because the relapse rate may increase significantly. An Australian group demonstrated that relapse rate increased by up to a factor 2 when the vitamin D blood serum level at the start of treatment with interferon- β was below 20 ng/ml. Above this level, the immunomodulatory effects of interferon β were enhanced (Stewart et al 2012). They also showed that IFN- β therapy is associated with greater production of vitamin D from sun exposure, suggesting part of the therapeutic effects of IFN- β on relapse in MS may be through modulation of vitamin D metabolism.

A similar behaviour is known with respect to the monoclonal antibody Tysabri (natalizumab³) (Scott 2013).

One study with patients under treatment with Fingolimod showed that patients with serum 25[OH]D \geq 40 ng/ml had a lower number of active lesions in brain RMI at baseline compared to patients with the lowest 25[OH]D levels (less than 20 ng/ml) (Ferre 2018). In another study was observed improved MRI outcomes on percent brain volume change and proportion of patients free of new/enlarging T2 lesions, and a trend of less depression in the 'daily users' of vitamin D supplement in patients treated with Fingolimod (Hongell 2018).

² The protection of the face is recommended in case of intensive sun light

³ Natalizumab is a humanized monoclonal antibody (ending -zumab) and selective inhibitor for adhesion molecules located on the surface of white blood cells. It inhibits the migration of white blood cells into inflammatory foci.



From today's perspective, the determination of vitamin D blood level and the elimination of deficiencies are necessary and mandatory before immunomodulatory action should be taken. This fact unfortunately only slowly finds its way into the standard neurological treatment.

In short

MS results from the interplay of different genetic and environmental factors. The risk of developing MS is multifactorial and consists of numerous protective and promoting factors that act on the organism from the time of development in the uterus. The risk of a vitamin D deficiency in every phase of life is significant and can be minimized!

As reported in detail above, it can be deduced from the current data that vitamin D influences the risk of developing MS and its course by influencing the inflammatory component of the disease. This has been demonstrated in epidemiological, clinical, radiological, immunological and genetic studies. The data situation is less clear for chronic progredient forms. There is still a lack of clear studies on the benefit of vitamin D in these forms of course. Finally, until further information is available, it is imperative that vitamin D deficiency be compensated until the above reference range is reached and this has been recommended for several years by leading specialists (Pierrot 2017, Marrie 2017).

The take-home messages

Vitamin D and sun have a decisive and modulating influence on the immune system

Vitamin D serum levels between 60 and 90 ng/ml are the target

Vitamin D supplementation 4000 - 5000 IU daily / Sun 10-15 min daily is recommended

Vitamin D supplementation alone is only half of the story. Sunlight is on the same level of importance

Be aware of the interaction between interferon- β or Tysabri[®] and vitamin D

Do under no circumstances start high-dose vitamin D level treatment (e.g. Coimbra protocol) without medical supervision (otherwise serious or even fatal damage to health may occur)



Relevant studies

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