Vitamin D Supplementation in the Fight Against Multiple Sclerosis

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Abstract

Multiple Sclerosis (MS) is an autoimmune disease in which the immune-mediated destruction of nerve axons and their protective myelin coating in the central nervous system results in a myriad of serious disabilities. One aspect of MS is the failure of the suppressor side of the immune system to contain autoimmune reactions. Vitamin D is an established immune suppressant and thus persons with MS want to ensure they have an adequate supply of vitamin D. This suggestion is underscored by abundant scientific data that link vitamin D deficiency to MS onset and progression. Such data include epidemiology, animal experiments, immunological studies and small clinical trials.

Recent literature reviews indicate that an average daily intake of 4000 IU of vitamin D from all sources, including sun exposure, oral intake and internal stores is required for optimal health. This result is similar to that deduced from an evolutionary biology perspective. The human genome evolved in a sunny, low latitude environment and is thus most compatible with a tropical supply of vitamin D that is in the range of 4000-5000 IU/d. For those living in latitudes above 40 degrees, a daily supplement of up to 4000 IU is likely necessary in the late fall and winter months to ensure optimal levels of circulating vitamin D are maintained all year around. To determine an appropriate vitamin D supplement level for their unique combination of genetics, latitude and lifestyle, one should determine their blood level of circulating vitamin D each year in the early fall.

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Introduction

Multiple sclerosis (MS) is a chronic, autoimmune disease that affects the central nervous system. It is driven by activated, autoaggressive T cells which lead an immune attack on myelin, the fatty substance that wraps around and insulates the nerve axons of the central nervous system. The progressive loss of myelin and nerve axons translates into the slow accumulation of multiple disabilities.

A variety of different supplements are recommended for people with MS and it is worthwhile to examine the science and logic behind any given supplement recommendation. Vitamin D, the sunshine vitamin, is not often strongly advocated for MS, although small dosages (~200-400 IU) are usually part of a total vitamin recommendation. Over the past decade a number of papers on the relationship between vitamin D and MS have been published.[1,2] On the basis of this information it appears that persons with MS could possibly significantly benefit from a substantially higher supplementation of vitamin D than is currently proposed in various self help books or suggested by clinicians.

I will present a brief discussion of vitamin D and follow that with the scientific evidence that supports the concept that vitamin D likely plays an important role in controlling autoimmunity and MS. Such evidence consists of epidemiological data, animal experiments, immunological analyses, genetics and the results of small clinical trials that used vitamin D or a metabolite as the therapeutic agent. When all the data are considered as a whole, it becomes apparent that adequate supplementation of vitamin D may well be beneficial and, given the very low cost and safety of such a therapy, persons with MS

might want to make sure they are receiving sufficient amounts each day.

The key questions of, how much vitamin D is needed, is this amount safe, and how can one best obtain this amount, are also addressed. Vitamin D is a fat- soluble vitamin and can be toxic in large dosages. Thus it is very important to examine current data in regards to vitamin D safety and reasonable sources of the vitamin. In the final part of the essay, vitamin D intake is examined in an evolutionary perspective and a summary on how vitamin D fits in the overall "Paleolithic Prescription" for MS concludes the article.

Vitamin D

A detailed discussion of the chemistry of vitamin D^3 is far beyond the scope of this article. A few points are worth mentioning to help one gain an appreciation of what vitamin D is, how it is activated in the body, and the role it plays in health and illness. The primary source of this nutrient is not from diet but rather from a chemical photolysis reaction in the skin. When ultraviolet B (UVB) radiation from the sun penetrates the epidermis, it is absorbed by a metabolite of cholesterol (7-dehydrocholestrol) that is then converted into vitamin D (calciferol). Notably vitamin D is biologically inert and is metabolized in the liver to produce 25(OH)D (calcidiol) that is the main form of circulating vitamin D. Although this substance is also inactive, its concentration in the blood provides a good assessment of a person's vitamin D level and the relationship of various levels of 25(OH)D to health will be discussed later. The final step in the vitamin D story is that 25(OH)D is converted to an active hormone, 1,25(OH)2D (calcitriol), in the kidneys and in other places throughout the body by the action of the enzyme 1,25 hydroxylase.

The main physiological role of vitamin D, through the actions of its metabolized hormone, calcitriol, is to regulate the amount of calcium and phosphorous in circulation. In this way it has a major impact on bone growth or lack thereof (rickets, osteomalacia) and, when most people think of vitamin D, they think of it in this context. When calcium levels are low (usually due to insufficient vitamin D and/or calcium intake), the body activates the parathyroid gland, which produces PTH (parathyroid hormone). This hormone kick starts vitamin D hormone production in the kidneys and helps to remove calcium from the bones so that it can be used in more important functions. Thus a measurement of PTH also provides a good proxy for vitamin D levels in circulation. When adequate vitamin D is available there is generally no need for the body to produce PTH and serum levels of this hormone are negligible.

As will be discussed below, recent research has uncovered more roles for vitamin D besides calcium regulation. The most relevant of these functions is as an immune regulator and this has obvious implications for its putative role in MS and other autoimmune diseases.

Scientific Data Relating Vitamin D to Multiple Sclerosis

Goldberg, using a variety of epidemiological data, first proposed the concept that vitamin D was an important factor in the onset and progression of MS.[4,5] Goldberg emphasized the conspicuous high prevalence of MS in areas that receive a relatively low amount of sunlight. The relationship between MS prevalence and sunlight had been documented earlier with a very impressive negative correlation between MS prevalence in American military personnel and hours of sunshine of their place of birth .[6] Goldberg[4] took the next step and postulated that such a close correspondence between low sunlight and MS was due to low vitamin D production in the population. Goldberg also showed that within areas of low sunlight (e.g. Norway) differences in MS prevalence could be explained by dietary factors that affect vitamin D pro-

duction. Such factors include the amount of fish eaten (increases vitamin D) and the amount of grains consumed (reduces vitamin D levels due to the action of phytates). To explain how vitamin D levels were related to MS, Goldberg[5] proposed that genetically susceptible individuals may need larger than normal amounts of vitamin D during myelin formation and that insufficient vitamin D during childhood might result in defective myelin that would be susceptible to breakdown in later life. Goldberg's ideas were completely ignored by medical researchers, although, as will be discussed later, he was able to organize a small clinical trial to test his concept.

Goldberg's innovative hypothesis that vitamin D explains the distinctive geographic variations in MS prevalence is even more attractive today than it was when first proposed 29 years ago. A recent study compared the large, unexplained variations in MS prevalence in Australia with the variations in the supply of ultraviolet radiation (UVR) (a close proxy for vitamin D supply) over the continent.[7] Australia is the ideal place for such a study because population genetics as well as other potential risk factors for MS, such as infectious agents and diet, are nearly constant. The lack of a genetic effect on MS prevalence in Australia was demonstrated by a study of that showed that geographic variations in MS prevalence rates in British and Irish immigrants closely matched the variable rates in native Australians.[8] Importantly, Australia spans over 30 degrees of latitude, from tropical Queensland to temperate Tasmania, and thus there is a large variation in UVR supply and consequent vitamin D supply over its extent.

Over Australia there is a very strong, negative correlation between MS prevalence and UVR supply (R = .91).[7] Notably this correlation was superior to the correlation between malignant melanoma incidence over Australia and UVR (R =.8). Given that it is accepted that UVR is the main causal factor in malignant melanoma, it is very difficult to escape the conclusion that UVR must also be an important factor in MS etiology. UVR most likely exerts a protective effect through the production of vitamin D. This interpretation is solidly supported by epidemiological data which show that in low sunlight areas such as Scandinavia and Canada, the only populations that have very low rates of MS despite genetic susceptibility are those which consume large quantities of fish and thus receive a "tropical" supply of vitamin D through their diet.[9,10,11] UVR supply has also been related to other cell-mediated autoimmune diseases such as type 1 diabetes and rheumatoid arthritis.[12,13]

Another significant epidemiological study which implicates vitamin D supply (through UVR supply) in MS etiology demonstrated that individuals who had the highest residential and occupational sunlight exposure had a substantially lower mortality risk from MS (odds ratio 0.24).[14] The beneficial effects of sunlight exposure as regards MS mortality risk were independent of country of origin, age, sex, race, and socioeconomic status. Also it has been demonstrated that the early spring nadir in vitamin D levels correlates with both the peak of MS lesion activity in German MS patients and the peak of MS disease onset in Switzerland.[15]

The very robust and convincing epidemiological evidence for the involvement of vitamin D in MS is matched by very diverse immunological data that also link vitamin D and MS.[16,17] This work began in the early 80s with the recognition that immune cells carry a receptor for the active hormone of vitamin D (1,25-(OH)2D) and that this hormone likely regulates immune functions.[18]

This discovery led to ongoing research efforts that continue to uncover a number of important ways in which vitamin D hormone affects the immune system.[19,20] One area of research in this regard is the experimental studies with mice and rats that are

genetically susceptible to animal forms of autoimmune disease such as EAE (closely resembles MS). These studies showed that injections of vitamin D hormone could protect against or arrest the animal forms of MS,[21,22,23] type 1 diabetes,[24] rheumatoid arthritis[25] and lupus.[26] Furthermore, immunological analyses done in conjunction with these experiments revealed the following immune-regulating actions for vitamin D hormone:

1) Suppresses antibody production by B cells and the proliferation of T cells in the thymus.[27]

2) Upregulates cytokines TGF-beta and IL-4. These proteins, which are produced by immune cells, act as suppressants of inflammatory T cells.[28,29]

3) Inhibits production of pro-inflammatory cytokines such as IL-1, IL-2, TNF and IFN gamma[30,31] which also reduces inflamammatory reactions.

4) Interferes with T helper function and inhibits the passive transfer of cellular immunity by Th in vivo[32]

5) Inhibits the production of NO (nitric oxide) by immune cells.[33] NO has been identified as one of the most destructive products of the immune system and is an important factor in demyelination.

6) Inhibits the proliferation of activated and memory T cells.[34, 35] Such cells are the main mediators of the inflammatory autoimmune reactions of MS.

7) Exerts immunomodulating effects in the CNS by inducing a profound downregulation of antigen expression by both infiltrating and resident antigen-presenting cells (e.g. macrophages).[36]

8) Inhibits the actions of antigen presenting dendritic cells.[37,38]

In summary, vitamin D hormone has numerous effects on the immune system and acts within the CNS. All of these effects have the combined result of significantly reducing inflammatory autoimmune reactions from occurring and they readily explain the impressive correlation between MS prevalence and vitamin D supply and why vitamin D hormone is so effective in suppressing a variety of animal autoimmune diseases including EAE (animal MS).[1,16,17]

Genetic data also implicate vitamin D in MS[39,40] although a Canadian study[41] did not find such an association.

Vitamin D has been used as a therapeutic agent in only a few small clinical trials. Notably Goldberg helped to organize a small trial in the early 80s.[42] Ten subjects took 5000 IU/day of vitamin D along with about 1000mg of Ca and 600mg of Mg for two years. The subjects acted as their own controls with the exacerbation rates during the trial compared with the subjects' historical rates of exacerbation. A notable decline in exacerbation rate was noted, although the small size of the trial makes the results equivocal. A more recent small baseline versus treatment trial using cod liver oil as a therapeutic agent also resulted in a reduced exacerbation rate (80% of participants were attack free over the two year trial period).[43] Larger, well-controlled trials involving MRI measurements are required to document the value of vitamin D supplementation for MS.

The results from a small clinical trial for rheumatoid arthritis and a vitamin D metabolite over a three-month time period were positive: "Therapy showed a positive effect on disease activity in 89% of the patients (45% with complete remission and 45% with a satisfactory effect). Only two patients (11%) showed no improvement, but no new symptoms occurred."[44] Also of relevance are studies which showed that high dietary vitamin D supplementation in infancy significantly reduced the risk of type 1 diabetes in later life.[45,46,47]

In summary, a variety of data, from epidemiology, animal experiments, immunological investigations, genetics and small clinical trials indicates that vitamin D supply is a major factor in MS etiology, most

likely through immune suppressant effects of vitamin D hormone. Thus its use as a supplement by persons with MS is clearly warranted and hopefully clinicians will see the need to counsel their MS patients on the importance of achieving and maintaining optimal levels of circulating vitamin D.

Supplementation and Safety

The above scientific data indicate that vitamin D plays a significant role in MS onset and progression and thus it seems only prudent for persons with MS to have a sufficient intake of vitamin D. In this section the questions of, how much, where to get it and is it safe, are addressed and are based on recent reviews[48-51] and a recent clinical trial which tested the effect and safety of daily supplementation with 4000 and 10,000 IU of vitamin D.[52]

Humans evolved for almost 4 million years under conditions of a relatively large supply of vitamin D, with a naked human in Africa likely getting at least 10,000 IU on sunny days.[48] Vieth[48] reviews all the literature on intake of vitamin D and resultant levels of 25(OH)D and PTH. The key here is it has been established that when adequate levels of 25(OH)D (an intermediate metabolite of vitamin D) are circulating there is no need for the body to produce PTH (parathyroid hormone). To achieve this, it is desirable to have 100-140 nmol/litre of 25(OH)D in circulation.[48] It appears a total supply of about 4000 IU of vitamin D a day is required to reach such a level of circulating vitamin D.[48] This conclusion is well supported by a recent study that concluded "Healthy men seem to use 3000-5000 IU cholecalciferol/d."[52]

As described earlier, the main source of vitamin D is the sun and in lower latitude climates (below 35 degrees) an average intake of 3000-4000 IU/d over a year is readily possible if an individual spends a reasonable time in the sun. However, in higher latitude, colder climates, like those of Canada, northern USA, northwest Europe and southernmost Australia, it is almost impossible to average 4000 IU a day because for four to six months of the year dermal synthesis is minimal to non-existent.[53] Even during the few hot summer months an individual would have to spend considerable time in the sun to achieve the required intake during that part of the year. Even those who are exposed to very high amounts of UVR during the summer through outdoor occupations and achieve optimal 25D levels at that time have much lower levels of circulating vitamin D by mid winter.[54]

Thus in higher latitude areas of low UVR supply, vitamin D supplements, especially during the "vitamin D winter months," are required to maintain an optimal level of 100-140 nmol/l. As Vieth[48] notes "From what is known now, there is no practical difference whether vitamin D is acquired from ultraviolet exposed skin or through diet." Cod liver oil, fish and vitamin D fortified foods are the usual dietary sources used to obtain vitamin D. However these sources usually supply much less than 1000 IU/day and do not have much effect on circulating vitamin D levels.[52,55] One can obtain specific vitamin D3 supplements that are usually small 1000 IU pills and a bottle of 100 costs between 5 and 10 dollars. This would seem to be the most reasonable source of supplemental vitamin D. Cod liver oil is another potential source and each teaspoon usually has ~ 400 IU. One advantage of this source is that it also provides substantial omega 3 EFA that is also potentially very beneficial for MS.[56] If this source is used, it is important to ensure that associated vitamin A intake from the cod liver oil remains reasonable.

The amount of supplementation that is required to achieve and maintain an optimal level of circulating vitamin D will vary somewhat depending on a person's genetics, geographic location and lifestyle. If one gets lots of sun exposure in spring and summer (April to October in the northern hemisphere), then supplementation will

only be required in late fall and winter (November through March in the northern hemisphere), if at all. It is important to realize that part of the vitamin D synthesized during the summer months is stored in tissue for later use.[52] Thus, if one gets plentiful sun exposure during summer, a winter supplementation level of 1000-2000 IU will be sufficient to maintain an optimal level throughout the winter. For those who do not get a lot of sun exposure and consequent vitamin D production during spring and summer due to a high latitude (>45) location, frequent overcast skies or sun avoidance, a 1000 IU supplement during these months and a 4000 IU supplement in the late fall and winter period should allow an optimal level of circulating vitamin D to be achieved and maintained.[48]

Vieth[48] also addresses the safety issue of vitamin D at length. He suggests that the "no observed adverse effect level (NOAEL)" is at least 10,000 IU/day and at a 25(OH)D level of 220 nmol/l. The European Scientific Committee on Food sets the NOAEL at 4000 IU/d and at a level of 200 nmol/l for circulating 25(OH)D.[51] Vieth[48] interprets the lowest observed adverse effect level (LAOEL) to be 40,000 IU/day. It must be emphasized that there have only been short term (up to 6 months) trials of supplementation with relatively high vitamin D dosages of 4000 and 10000 IU[52,57] and there have been no studies of possible adverse effects of long term, moderately high levels of circulating vitamin D (175-300 nmol/l). Given that almost everyone gets some vitamin D from sun exposure in summer and that a total of 3000-4000 IU is all the body uses in a day, one does not want to take supplemental dosages of 4000+ IU over an extended period of time. The combination of sun exposure and such supplementation would logically result in a yearly oversupply of vitamin D and a consequent continually rising level of circulating vitamin D that might well exceed the accepted safe limit for circulating vitamin D (200 nmol/l) within a few years.

Because it is difficult to know how much vitamin D one is receiving from the sun and because of genetic differences in vitamin D synthesis and usage, the best course of action for a person with MS is to initially use the above supplement recommendations and to arrange for a 25(OH)D test in the early fall (October in the northern hemisphere). If one's 25(OH) D level exceeds 140 nmol/l at that time, then no supplementation is needed until the situation is reassessed a year later. For those with an optimal level between 100 and 140 nmol/l, 1000-2000 IU of supplementation would be appropriate during the "vitamin D winter". For those with 25(OH)D levels below 100 nmol/l, a 4000 IU supplement level in the late fall-winter interval with a 1000 IU in the following spring and summer months would be suitable. Basically one wants to ensure that their level of circulating vitamin D rarely, if ever, falls below 80 nmol/l or rises above 175 nmol/l. This is best achieved by a yearly 25D test and, based on that result, an appropriate supplementation regimen for the next year.

It appears that adequate calcium and magnesium intake must accompany vitamin D supplementation for vitamin D to have its maximum effect.[42] It was recently demonstrated that calcium levels strongly affect the action of vitamin D for suppressing EAE in mice.[58] Calcium intake from foods and supplements should be in the range of 800-1200 mg/day with magnesium intake being about half this.

In summary, a daily availability of vitamin D of ~ 4000 IU from dermal synthesis, oral intake and internal stores is required for the attainment and maintenance of an adequate level of circulating vitamin D and consequent actions of synthesized vitamin D hormone. Vitamin D, through the actions of its metabolites and in combination with adequate calcium and magnesium, plays an important role in the suppression of autoimmune reac-

tions. Thus the maintenance of an adequate supply of vitamin D is especially important for those with MS.

Vitamin D in an Evolutionary Perspective

Eaton and Konner[59] hypothesized that, with the advent of agriculture and the subsequent industrial and technological revolutions, consequent changes in dietary habits and major shifts in the intake of various nutrients have adversely affected human health. They suggest that these major changes are in part responsible for a myriad of "genetic-environmental" diseases including heart disease, stroke, type 2 diabetes and various forms of cancer and this concept has been extended to autoimmune diseases by Cordain.[60,61] In this context it is useful to examine changes in vitamin D intake during the four million year evolution of human beings and how such changes are related to the rise of MS.

Humans lived exclusively in low latitudes and consequent hot climates throughout most of their evolutionary development and thus they experienced a relatively large intake of vitamin D from abundant UVR from sunlight. Natural selection would have ensured that the human genome became very compatible with such an intake, estimated to be in the range of 4000-6000 IU/d . This would have resulted in circulating concentrations of 25(OH)D of between 100 and 140 nmol/litre which, as discussed above, is regarded as the range of the optimal level of circulating vitamin D. Such a concentration supplied all the vitamin D hormone required for a variety of functions including the maintenance of a strong skeletal structure and the control of autoimmune reactions induced by foreign antigens derived mainly from infectious agents. The importance of adequate vitamin D for human health is underscored by the fact that evolution produced a very simple and seemingly fail-safe method for its attainment.

As humans migrated out of Africa into temperate areas, less sun-derived vitamin D became available and daily intakes likely fell somewhat. However, because long periods were spent outside hunting and gathering, most Paleolithic people still obtained sufficient vitamin D (3000-4000 IU/day) and readily maintained an adequate serum concentration of 25(OH)D throughout the year.

With the advent of agriculture about 8000 years ago and the ensuing population explosion, maintaining adequate levels of vitamin D and its metabolites started to become a problem for the first time in human history. Population pressures forced humans to migrate into even more hostile areas in terms of cold climates and low sunlight. They also tended to eat less fish and spend much more time out of the sun. Significantly, two of the main foods of agriculture have an adverse effect on the action of vitamin D. Grains, which are the number one food of agriculture, contain phytate or phytic acid which counters the action of vitamin D.[60,62] Notably, areas where grains were grown in Norway tended to have the highest rates of MS.[4]

Another food introduced into the human diet by agriculture is milk. Milk may also have an adverse effect on vitamin D by affecting the vitamin D receptor on cells. Part of the bovine albumin protein of milk is a molecular mimic of the vitamin D receptor.[63] Thus an immune reaction against that milk protein can potentially result in an autoimmune reaction against the vitamin D receptor. This would significantly lower the effectiveness of vitamin D hormone to bind with a variety of cells (including immune cells) and carry out its important functions.

Our modern lifestyle has only exacerbated the problem of vitamin D deficiency and large populations now inhabit low annual sunlight areas. The consumption of fish is very low in many agricultural areas where diets are completely dominated by high phytate, gluten grains and dairy prod-

ucts. A dominance of indoor jobs, fears of skin cancer and the use of sunscreens have reduced exposure to sunlight further such that, even in summer, many people do not get anywhere near the required vitamin D intake from sunlight. Thus it would appear that chronic vitamin D deficiency for much of the year (<75 nmol/litre of 25(OH)D) is a Neolithic problem for large populations which live in low sunlight climates. The cause of the problem is a variety of lifestyles factors which greatly differ from those of the Paleolithic when adequate vitamin D was readily obtained.

Notably persons with MS tend to be at the problematic end of the deficiency spectrum (<50 nmol/l 25(OH)D). The reasons for this higher than normal deficiency is likely multifold and includes the tendency for persons with MS to spend less time outside doing various laborious or sporting activities, the use of steroidal drugs in treatment, diets with an abundance of grains and milk and no encouragement from their doctors or MS societies to take sufficient vitamin D supplements. A study of 80 persons with MS revealed a mean level of 25(OH)D of only 43 nmol/litre with a quarter of the subjects "having frank vitamin D deficiency (<25nmol/l)."[64] Not surprisingly the bone mineral density of most of the subjects was very low. Sadly, this study indicates that many people with MS likely do not have enough vitamin D intake to maintain their bones let alone to counter autoimmune reactions.

With both the general evolutionary perspective and the documented low levels of vitamin D in persons with MS in mind, it is worth discussing the role vitamin D plays in the overall development of MS. First of all it is important to differentiate between autoimmunity and autoimmune disease. Autoimmunity is the production of immune cells that are autoaggressive and such a phenonomen has most probably been present throughout human development. It is well established that autoaggressive immune cells are produced during infections[65] and the reason for this is that the body must maintain a vast repertoire of immune cells to ensure protection against a huge number of pathogens. Thus the common occurrence of cross-reactive immune cells that react against both foreign and self-antigens represents an evolved compromise between maximum protection against foreign invaders and maximum protection against autoimmunity. Through the actions of the suppressor side of the immune system, evolution has also ensured that the sporadic production of autoaggressive immune cells due to random infections would not go unchecked and result in uncontrolled autoimmunity. Such runaway autoimmunity is called autoimmune disease. Thus, although autoimmunity has always been with us, autoimmune disease is likely a relatively new phenonomen in human development.

The best explanation for the recent rise in autoimmune disease is that new environmental agents have upset the delicate balance between the production and suppression of autoaggressive immune cells by both increasing autoimmune reactions and by hindering the control of such reactions. In an environment of increased autoimmune reactions and decreased suppression, autoimmunity can progress to autoimmune disease in genetically susceptible people. The profoundly different dietary regimen, which began with the adoption of agriculture, is one obvious source of such new, immune-disruptive agents. Fruits, vegetables and lean wild meats that had a low and balanced fat content dominated the Paleolithic diet. The main foods "recently" introduced by agriculture are grains (i.e. grass seed), dairy products and meat from domesticated animals that has very high saturated fat content. It would appear that proteins from various foods introduced by the Neolithic agricultural revolution (e.g. gluten, dairy, legumes) result in autoimmune reactions mainly by increasing intestinal permeability and by mimicking infectious and self-antigens.[60,61,66]

Such food-driven autoimmune reactions, although of relatively low magnitude in comparison with infection-driven autoimmune reactions, occur almost on a daily basis. They have a significant cumulative effect and thus recently introduced foods are clearly suitable candidates for the agents that result in harmless autoimmunity becoming problematic autoimmune disease in genetically susceptible persons.

This increase in Neolithic dietary elements that contribute to autoimmune reactions is matched by a notable decrease during the Neolithic of nutrients that play a significant role in the suppression of autoimmune reactions. These suppression-inducing nutrients include both omega 3 essential fatty acids (fish oil)[55,67] and vitamin D as discussed herein. Thus the newly adopted dietary habits of agriculture promote autoimmune disease both by increasing autoimmune reactions and by blunting anti-inflammatory responses. Not surprisingly, MS and other autoimmune diseases are most common in areas where the dietary regimen contains a dominance of pro-inflammatory food types and a paucity of anti-inflammatory nutrients. The common deficiency of vitamin D is just one of the Neolithic nutritional factors which, in combination with the ever-present infectious agents, result in a variety of autoimmune diseases in these areas. Consequently, it is just one of a number of factors which must be reversed if one hopes to successfully combat an autoimmune disease such as multiple sclerosis.

As discussed above, it appears the best method of reversing vitamin D deficiency is to use an appropriate supplement of vitamin D which, combined with sun exposure, will result in optimal levels of vitamin D metabolites. This in turn should result in increased suppression of autoimmune reactions precipitated by food and infectious agents and help to turn the tide against uncontrolled autoimmunity.

Summary

An abundance of scientific evidence indicates that vitamin D deficiency is associated with MS onset and progression. Such evidence includes epidemiology which demonstrates that high prevalence rates of MS closely track areas of low intake of vitamin D. Animal experiments reveal that vitamin D hormone can suppress a variety of animal autoimmune diseases including EAE, the animal equivalent of MS. Furthermore, associated immunological studies have shown that vitamin D hormone has a number of immunomodulating functions, all of which contribute to the suppression of inflammatory autoimmune reactions. Small clinical trials have suggested that vitamin D has some efficacy in slowing autoimmune disease progression although no properly controlled trials have been conducted.

The optimal, average daily supply of vitamin D from all sources, which includes sun exposure, some foods, supplements and internal stores is about 4000 IU/d. This results in a circulation concentration of 25(OH)D (a vitamin D metabolite) of 100-140 nmol/l and this level is required for the proper functioning of all vitamin D-dependent systems. In colder, low sunlight areas such an intake from the sun is impossible for at least half the year and it is important to use supplements to makeup the shortfall in vitamin D supply. Currently suggested supplement levels of 200-400 IU are much too low. A daily supplement of 4000 IU of vitamin D in late fall and winter and 1000-2000 IU in spring and summer seems warranted for people who do not get a lot of exposure to sunlight in the summer months. It is important to determine one's 25(OH)D level each year in early fall to allow an appropriate supplementation regime to be established for the next 12 months. This will ensure that one's circulating vitamin D level remains optimal throughout the year and does not fall below 75 nmol/l or rise above 175 nmol/l.

Throughout most of the four million years of human development, humans had a relatively high supply of vitamin D (~4000-5000 IU/day) due to abundant sun exposure. Major environmental changes brought on by the agricultural, industrial and technological revolutions greatly reduced sun exposure and resulted in large populations in high latitude areas experiencing a subclinical and chronic vitamin D deficiency. Vitamin D deficiency is just one of the major nutrient-related factors which play a role in multiple sclerosis. Notably the dietary regimens which contain the most pro-inflammatory food types (e.g. gluten, dairy) and the least anti-inflammatory nutrients (vitamin D, omega 3 fats) occur in areas in which MS and other autoimmune diseases are most common. To combat MS, a person must change their lifestyle with diet revision being perhaps the most useful modification. As part of this change, it is important to ensure that sufficient vitamin D (4000 IU/day) is available, through sun exposure and supplements, for the production of active vitamin D metabolites.

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