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Vitamin D and multiple sclerosis: timing of sampling, treatment and prevention

“With today’s knowledge, it is the authors’ view that enough scientific data exist to suggest that multiple sclerosis patients should be informed about the association between vitamin D levels and multiple sclerosis inflammatory disease activity.”

KEYWORDS: autoimmune diseases ■ biological specimen banks ■ multiple sclerosis ■ prospective studies ■ risk factors ■ vitamin D

There are several associations that intriguingly indicate a protective role for the sunshine vitamin, vitamin D, in multiple sclerosis (MS) etiology [1,2]. Long ago the epidemiological observation was made that the incidence of MS increases with greater distance from the equator. The simplest explanation for this would be that differences regarding climate, and most obviously sun exposure, account for this observation. The epidemiological data that suggest an environmental factor are further strengthened by migration studies, which show that an individual’s risk for MS decreases if he or she moves from a high- to a low-risk area [3].

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Although these observations are several decades old, the protective effect of sunshine regarding MS is often still seen as just a hypothesis. Several circumstances may have contributed to delay focused research and the recognition of this association: many MS patients avoid sun exposure since this may worsen their symptoms (a raised body temperature produces a transient increase of old symptoms); the anti-sun exposure propaganda driven by the governmental authorities; an inherent problem with migrant study interpretation, where focus has been on methodological problems instead of on the resulting epidemiological pattern; and a long prevailing genetic-oriented paradigm, which suggests that results suggesting environmental risk factors are unreliable and are probably explained by genetic factors.

The demonstration of vitamin D-related genetic associations has helped to persuade many skeptics. A causal role for vitamin D is suggested by the presence of an association between rare loss-of-function mutations in the gene *CYP27B1*, which encodes the enzyme that converts vitamin D to its active form, and MS risk [4].

Three prospective studies suggest a protective role for vitamin D. In two studies, 25-hydroxyvitamin D (25[OH]D) levels were analyzed in biobank blood samples drawn before MS onset. A protective effect by higher 25(OH)D levels was demonstrated (62% decreased risk for >99 nmol/l vs <63 nmol/l [5], and a 61% decreased risk for ≥75 nmol/l vs <75 nmol/l [6]). Furthermore, a daily intake of ≥400 IU vitamin D was associated with a 41% decreased risk for MS [7].

A very similar pattern with an association between vitamin D and disease risk has been demonstrated for another autoimmune disease, Type 1 diabetes mellitus. There are genetic, prospective biobank and vitamin D intake data that all suggest a protective role for vitamin D in Type 1 diabetes mellitus etiology [8–10].

Among MS patients, a clear association is present where higher vitamin D levels are associated with a lower risk for inflammatory activity [11]. Higher vitamin D levels also decrease the risk of developing MS in patients who have experienced a first relapse but do not fulfill the MS diagnostic criteria [12]. These observations have been made in both adults and pediatric patients. Currently, the results from the largest randomized controlled trials (RCTs) with vitamin D supplementation in MS are negative regarding primary outcome efficacy measures, but the studies are small and indicate the possibility of a treatment effect [13]. To our knowledge, there are now seven larger RCTs in progress,



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which are evaluating the effect from vitamin D supplementation in MS.

The results above suggest that the MS incidence would have been 60% lower if vitamin D levels in the western world were higher. Skeptics doubt this as genes do not change and we must avoid sun exposure due to the risk of skin cancer. Although many would prefer sunshine rather than another pill, there are no convincing data that show the protective effect of sun exposure on MS risk is not mediated through vitamin D. Studies suggesting vitamin D-independent effects from sun exposure may not have taken temporal aspects of the exposure estimates into full account [14,15].

Vitamin D believers hope that the protective effect from vitamin D is even higher. In the two prospective biobank studies referred to above, a stronger protective effect (~90% lower MS risk in those with higher vitamin D levels) was seen in the subgroups of young individuals.

Although a questionnaire study suggested that a higher maternal vitamin D intake would have a protective effect against MS in the offspring [16], the only prospective study using gestational biobank sample analyses to address this issue failed to find an association [6]. However, the latter study only included samples drawn during early pregnancy and the sample size was small.

Why is vitamin D a stronger risk factor in samples drawn around the age of 20 years? It may simply be a spurious finding in post-hoc analyses. It is also possible that this younger population differs in some other aspect. In our prospective biobank study, the young subgroup had an earlier disease onset. Since the same pattern was found in two studies, we must consider a third explanation, and that is that timing of blood sampling is crucial when environmental factors are studied.

Consider samples drawn after diagnosis in a study of environmental etiological risk factors. Post-diagnosis associations may derive from reversed causation. The same objection applies, although to a lesser extent, for samples drawn after symptom onset but before diagnosis. Even with samples drawn just weeks-to-months before MS onset, it is probable that the level of a particular environmental risk factor merely serves as a proxy for previous levels that were present when the disease process actually started. That was when the risk factor was pathogenically most active. We conclude that prospective samples (i.e., those drawn before MS symptoms), are needed – but when should these be drawn? At 1, 5, 10 or 20 years before MS onset, or is it more appropriate to ask at what age these should be drawn?

A common view among MS researchers is that the disease process starts during adolescence, around the age of 15 years. This notion is several decades old and comes from migrant studies but has received further support in recent years where several factors that influence MS risk – all possibly linked to vitamin D status – seem to be present only during adolescence but not later: shift work, BMI and, for Norwegians, time spent outdoors [17]. There are also register data on infectious mononucleosis sex ratio showing a female surplus (as in MS) only in the age range 10–14 years [18].

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Therefore, in a prospective study on prototypic MS, samples estimating environmental risk factors should ideally be drawn during adolescence. Analyses have to include the most important MS risk factors to enable risk interaction calculations: smoke exposure (serum marker cotinine), HLA status, 25(OH)D levels and antibodies against Epstein–Barr virus (EBV). Among these risk factors, vitamin D and EBV have a leading position as having the largest impact on MS risk. It is therefore logical to identify samples drawn at primary EBV infection – infectious mononucleosis – in persons that later develop MS, and to study the impact of these risk factors at that point in time [19]. The most interesting hypothesis is the interplay between EBV and vitamin D: do 25(OH)D levels at primary EBV infection affect future immune control of latent infection? In Sweden there is the possibility to perform such a study. Our recently launched project, DEMOS (vitamin D and EBV – infectious mononucleosis – in multiple sclerosis etiology), aims to identify 1000 prospective MS samples collected at a young age (approximately a third drawn during childhood-adolescence). We will especially look at samples from virological biobanks drawn during infectious mononucleosis.

With today's knowledge, it is the authors' view that enough scientific data exist to suggest that MS patients should be informed about the association between vitamin D levels and MS inflammatory disease activity. Since vitamin D supplementation (2000 IU [50 µg] vitamin D3 [cholecalciferol] per day) is not harmful or expensive, this treatment should be recommended and

patients informed that definite results from RCTs are pending [1,20]. The aim is to reach 25(OH) D levels ≥ 75 –100 nmol/l. These levels are rarely seen in nonsupplemented patients in northern Sweden and may therefore be regarded as unnatural, implying that long-term side effects may occur. On the other hand, these levels may be regarded as more natural since they approach levels in natives in Africa, where the human species once evolved. As for primary prevention, RCTs are desirable but may not be feasible even in MS first-degree relatives due to the large sample size and long follow-up needed. Although there are no direct scientific data supporting the use of vitamin D supplementation in children of persons with MS, who have a several-fold increased risk for MS, supplementation appears even more logical based on the data presented above. Such primary prevention cannot be recommended in the traditional sense, but physicians who treat

MS patients have the opportunity to inform parents with MS about the fairly strong rationale providing indirect support for giving vitamin D supplementation to their children. Data on the use of vitamin D supplementation may be collected prospectively, and the risk of developing MS in supplemented and nonsupplemented children can be compared after 10–20 years of follow-up.

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