Mapping the effects of vitamin D in multiple sclerosis

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Vitamin D was discovered in the context of rickets, a disorder characterized by skeletal deformities. Scientists began searching for food that could prevent rickets, based on the knowledge that diseases as scurvy could be prevented by certain nutriments as citrus fruits. This led to the finding that the development of rickets was related to a dietary deficiency of a fat-soluble factor, in for instance butterfat or cod-liver oil. Another observation had led to the idea that sunlight exposure could prevent and cure rickets. Following this line of thought, parallel to the food experiments in the early 1920's, it was discovered that artificial sunlight could be used for prevention and therapy of rickets. Both therapies came together when it was found that also (vegetable) food irradiated by UV light could ameliorate rickets in rats. These experiments with irradiated food eventually led to the discovery of the chemical structure of the anti-rickets substance, called vitamin D. From the path to the discovery of vitamin D it is clear that (combined) findings from previous research help to develop knowledge and therapies. New answers lead to new questions, but also to new ideas (innovation) and new utilizations (application): today vitamin D is not only widely used to prevent rickets, but because of its observed pleiotropic effects vitamin D is also studied in many other diseases, including multiple sclerosis (MS). In MS, in particular the immune modulating properties of vitamin D could be beneficial. This valorization chapter elaborates on the relevance of our studies, and the value and the implications of our findings with respect to innovation and application.

MS is a chronic disease, which progresses over time with accumulating discomfort and disabilities. It is estimated that 2.3 million people worldwide have MS, and in the Netherlands this concerns approximately 17,000 people, which is almost 1 in 1000 citizens. Although most patients in early phases of disease do not (yet) have persistent neurological deficits, exacerbations are unpredictable and can be very disabling. In later stages, patients may increasingly lose their self-sufficiency (and sometimes self-conceit), as they may increasingly need medical care and devices such as braces or wheelchairs, and assistance from others. Furthermore, as the onset of the disease generally is in the reproductive age, physical and emotional burden because of the disease, but also therapies may affect family life (choices). Moreover, fatigue and depression and cognitive problems, which may start relatively early in the disease course, can have a considerable impact on daily life and quality of life. It is also because of these symptoms that people are less and less able to participate in social and economic life. Obviously, for society, the latter adds up to the high health costs. Altogether, MS is a disease with major consequences for the often relatively young patient, and which makes the patient call upon her or his relatives/close circle and society in several stages of the disease.

Unfortunately, a curative treatment for MS is not available. Most current therapies are
efficacious by reducing disease activity and preventing relapses, but do not have clear effects on disability progression. Our research team started its research on vitamin D in MS in 2008 with the aim to assess whether vitamin D supplementation could be an additional therapy in MS. This was inspired by the then limited evidence from association studies, pointing at a role for vitamin D in the development and disease course of MS, and small pilot studies with supplementation of vitamin D hinting towards a beneficial effect on certain clinical outcomes. Compared to the available therapies for MS at that time, the ‘injectables’, vitamin D supplementation could be an inexpensive, relatively safe and easy-in-use additional therapy. Although since 2008 there has been quite a forge ahead in the field of MS therapies, with an enormous expansion in, mostly orally administered, therapies targeting several aspects of the immune system, none of them has the ‘X-factor’. Most of the current therapies are expensive (€14,000.00 - 50,000.00 per year per patient), and carry relatively high risks on adverse events such as infections. With respect to vitamin D, much support has been obtained since 2008 for a beneficial role in MS and the safety of its use, to which our studies also have contributed. We have conducted several studies over the past decade in order to assess which clinical outcomes are influenced by vitamin D, as well as studies in order to assess which mechanisms underlie the observed beneficial effects. Our studies, including those presented in this thesis, are particularly relevant to settle which patients might actually benefit from supplementation with vitamin D, but may also be useful in the search for biomarkers for treatment initiation/ follow-up and for generating optimal supplementation regimens. Also, they may contribute to our insight in the disease process of MS. Therefore studying the role of vitamin D (supplements) in MS is relevant, mostly for the patient, but probably also for society; vitamin D supplementation will not replace other disease modifying therapies, but it is not inconceivable that (early) add-on vitamin D supplementation, by reducing MS disease activity, results in reduced non-attendance at work and reduced health care consumption. However, future studies need to confirm this, and have to show long term consequences.

**Observation to Innovation**

The studies of our research team of the Academic MS Center Limburg have been initiated and continued with the hope to find evidence that vitamin D supplements positively influence the disease course of MS, and therefore could be introduced in existing treatment strategies for MS. Over the years, we have followed the path from observational studies to clinical trials, an important step in the valorization process. In this thesis mainly data obtained by randomized supplementation trials have been used to solve our questions with respect to immunological effects of vitamin D, to understand its mechanism of action, and with respect to its role in depression in MS (chapters 2, 4, 5 and 7). At this point, we do not have supporting evidence that vitamin D supplementation can be used as an additional therapy to reduce depressive symptoms in MS (chapters 5 and 7). However, our other studies support the idea that vitamin D regulates immunological processes in early relapsing remitting (RR) MS (chapters 2 and 4), maintaining immune homeostasis, which may be underlying the observed clinical effects. Indeed, there is now increasing and convincing clinical evidence that vitamin D supplements (as add-on therapy to interferon-β1a) influence disease activity in early MS, although we still need additional studies for clear therapeutic regimens.
Nonetheless, positive results have been spread and (tentative) implementation of vitamin D supplementation for MS in clinical practice has already been started, also in the academic MS center Limburg.

Not only from a medical point of view, but also scientifically our studies may contribute to innovation or new concepts. With respect to the immunological processes in MS, our studies have shown that deviations or deficits progress in early MS after disease onset (chapter 2). These may lead to sustained immune disturbance and disease activity, and therefore interference in this dynamic course in early disease may pay off. Another interesting finding is the specific drop in anti-EBNA-1 antibody levels (chapter 4), which could fit in the concept of interaction between vitamin D and the Epstein-Barr Virus (EBV) in MS. Better understanding of this potential interaction and of the dynamics of the immune system in early MS is needed. Furthermore, results of our in vitro and in vivo studies, have redirected our attention to the fact that vitamin D is only one player in a very complex network of nuclear receptor ligands (chapter 6). This concept asks for studies with a more holistic approach, enabling us to better translate knowledge to therapies and to better understand the (immune) pathophysiology of MS.

**OBESERVATION TO TRANSLATION: TARGET GROUPS**

Our research findings are primarily of interest for patients with MS, clinicians treating MS and scientists studying MS. Particularly patients in an early phase of MS may benefit from vitamin D supplements, as our team observed in these patients a beneficial effect of high-dose vitamin D supplements on MRI activity and, less pronounced, relapse rate. Also, our results suggest that, in early MS patients vitamin D supplementation may delay progression and prolong the RRMS phase (chapter 1). Although most findings do not support an effect of vitamin D supplements on disease activity and disability progression in later stages of MS, data on effects on specific symptoms, such as depressive symptoms or cognitive problems, in later stages of MS is still limited. To clinicians our data may be useful in order to advice their patients. Although our studies do not provide a clear supplementation regimen for patients with MS, and additional research is necessary, they do provide some answers with respect to the target population and vitamin D dose that can be used safely. As we broadly examined the role of vitamin D in MS, not only scientists within the field of MS research, but also in fields of other autoimmune diseases, basic (human) immunology, psychiatry and (neuro) endocrinology may appreciate our findings. Our studies contribute to the understanding of the role of vitamin D in the disease mechanism of MS, but also in immunological as well as neuroendocrine mechanisms in general. Furthermore, they may contribute to a better understanding of the overall pathophysiology of MS, and may inspire to study further the role of environmental factors in MS, such as the interaction between EBV and vitamin D, the dynamic course of the immune disturbances in early disease, and interplay of nuclear receptors in immune responses and neurodegeneration and neuroregeneration.
Before vitamin D supplementation can be approved for treatment of MS and can be applied in a clinical practice, relevant questions to be answered are: ‘What can we expect on the short and the long term from the therapy?’; ‘Who is eligible for the therapy?’ and, How do we prescribe the therapy?’. Currently, these questions have been answered partially by studies (RCTs) on in vivo effects of vitamin D in patients with MS. To be able to fully answer these questions, however, other insecurities with respect to vitamin D supplements and difficulties in studying vitamin D effects (Box 1) need to be addressed or solved in additional (clinical) studies. Long term follow-up of patients who participated in vitamin D supplementation studies will have to determine whether the observed effects on disease activity last and whether early vitamin D supplementation influences disease progression. In addition, future studies need to assess whether and for which population preventive supplementation is to be considered. Furthermore, to increase current evidence for effects of vitamin D on targeted disease outcomes we need more randomized controlled trials. In particular since there is a tendency to over-interpret the results of the many association studies, in which reverse causality and confounding are hard to exclude. Also, we need to be aware that all observations to a certain extent are biased towards the observer’s expectations or hopes; studies are designed based on certain hypotheses. Therefore, observer bias can be a problem when only is observed what is expected, or when findings are fit into hypothesis in the scientific presentation of results. Additionally, a lack of knowledge of the observer may (unintentionally) cause bias, as we only observe what we recognize. Although we have tried to avoid observer bias by conducting randomized controlled trials, and by studying (and presenting) effects on several cell subsets, also some of our interpretations will be biased: We may have wanted to see the positive findings too much, such as the reduction in cortisol awakening responses (chapter 7). Or we may have zoomed in too much on certain markers, such as CD25 or anti-EBNA-1 IgG (chapter 2 resp. 4), although these results have been replicated in separate cohorts.

In conclusion, the results of the studies of our team have brought us a bit closer to realization of vitamin D supplementation in MS, by answering some relevant questions regarding who and why. However, it is essential that clinicians and policy makers have a critical (re)view at the evidence for vitamin D effects in MS, and that additional research is conducted in order to solve the several questions mentioned, before vitamin D supplementation, exceeding generally advised daily dosages, is implemented in the standard of MS care.
### Box 1 - Vitamin D supplementation in MS: insecurities and difficulties

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<thead>
<tr>
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<th>Insecurities</th>
<th>Difficulties</th>
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<td><strong>Why?</strong></td>
<td><strong>Evidence</strong>&lt;br&gt;Endpoints, <em>i.e.</em> disease activity, disease progression, and symptoms.</td>
<td><strong>Study design</strong>&lt;br&gt;Association <em>versus</em> causality, <em>in vitro</em> <em>versus</em> <em>in vivo</em>; animal <em>versus</em> human, follow-up duration.</td>
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<tr>
<td><strong>Who?</strong></td>
<td><strong>Target population</strong>&lt;br&gt;Patient characteristics, <em>i.e.</em> sex, age, disease duration, disease phenotype / course.</td>
<td><strong>Identification/selection of targets</strong>&lt;br&gt;Genetic profile, biomarkers, effect modifiers (<em>i.a.</em> other nuclear receptor ligands)</td>
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<tr>
<td><strong>What?</strong></td>
<td><strong>Vitamin D status</strong>&lt;br&gt;Measurement of vitamin D, <em>i.e.</em> target level (deficiency/ sufficiency) method, metabolite, blood/CSF</td>
<td><strong>Technical issues</strong>&lt;br&gt;Circulation <em>versus</em> CSF <em>versus</em> target organ, metabolites</td>
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<td><strong>How?</strong></td>
<td><strong>Supplementation strategy</strong>&lt;br&gt;Treatment regimen, <em>i.e.</em> effective dose, fixed/variable dose, combination therapy.</td>
<td><strong>Safety</strong>&lt;br&gt;Efficacy <em>versus</em> side effects</td>
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