Hype or hope? Vitamin D in multiple sclerosis

Valorisation

Introduction

In the final chapter of this thesis, we will elaborate on how to make the knowledge, obtained in our scientific research and reported in this thesis, work. What can our results add to society, to whom, with whom and how? From a scientific point of view, there are still a lot of open questions in the field of multiple sclerosis and auto-immunity. The MS society in the UK tried to identify a top 10 of important research questions that are most crucial to be solved according to people having MS and their health professionals. [378]

- Which treatments are effective to slow, stop or reverse the accumulation of disability associated with MS?
- How can MS be prevented?
- Which treatments are effective for fatigue in people with MS?
- How can people with MS be best supported to self-manage their condition?
- Does early treatment with aggressive disease modifying drugs improve the prognosis for people with MS?
- Is vitamin D supplementation an effective disease modifying treatment for MS?
- Which treatments are effective to improve mobility for people with MS?
- Which treatments are effective to improve cognition in people with MS?
- Which treatments are effective for pain in people with MS?
- Is physiotherapy effective in reducing disability in people with MS?

Besides the effectiveness of vitamin D supplementation, at least three others questions among these 10 questions were touched upon in this thesis. Behind these questions lay a couple of even more basic questions about the disease mechanism in MS. How would it be possible to prevent MS, or to treat disability, fatigue and cognitive problems, if we still don't know what exactly happens in the pathophysiology, if we do not know what we measure and if we do not know how to measure it? In the question about the role of vitamin D we have made some important steps forward in the last years, investigating the disease mechanism and the clinical outcomes. Now, it is the question how we can continue to valorise these results in a process of value creation and making scientific knowledge available by translation, application, interaction and inspiration. [379, 380]

Translating from bench- to bedside: vitamin D in multiple sclerosis

Purpose of studying the role of vitamin D in MS

As has been described in the general introduction of this thesis, vitamin D deficiency has been associated with different diseases. [1] One of the diseases associated with a vitamin D deficiency, especially during childhood and adolescence, is MS. [70] Two main important scientific challenges in MS are to unravel the pathological mechanism and to develop new effective therapies with a minimum of (serious) side effects. While vitamin D deficiency has been identified as a risk factor for developing MS and has been proposed as a(n add-on) therapy decreasing disease activity, studying vitamin D in MS is very interesting from a scientific point of view.

Furthermore, there are other important reasons to study the role of vitamin D in multiple sclerosis. MS is a disabling disease mainly affecting young women, and to a lesser extent men, in the prime of their lives, many of them raising kids. Therefore, this disease will not only affect the physical and economic independence of those people but also of the people surrounding them, and of society. In the Netherlands, the total health costs for MS were 244 million euro in 2011 (0.3% of total costs spent in the healthcare). [381] Patients with MS experience physical disability with the need for a walking stick or wheelchair on average 20 years and 30 years after diagnosis, respectively. [382] Already at the time of a first clinical attack, 50% of the patients have cognitive impairment in at least two cognitive areas. [383] Together this involves a significant emotional and social burden: more than 50% of patients with MS have to decrease the amount of hours that they work or have to change to other functions [384] and they have higher probabilities to separate or get divorced compared to the general population [385]. Until now, there is no cure available and treatment focuses on the prevention of relapses and disability progression. Vitamin D could possibly be an interesting and relative cheap target for prevention and treatment of MS. However, last years, vitamin D has become a hype, and has sometimes been presented as the new panacea. With that it has become increasingly difficult to get to know the truth about the efficiency of vitamin D supplementation. Patients and their treating physicians want to know whether or not they should prescribe or take (high dose) vitamin D supplementation and when and in which dose. Policy makers need to know what choices they should make in preventive medicine and also funding bodies, who have to divide research budgets among a number of projects, need to be able to identify the most important research. All these decisions should be based on facts, not on hypes. We aimed to increase our knowledge about the role of vitamin D in multiple sclerosis, by collecting scientific data of well-considered research.

Main results described in this thesis which need further valorisation

In this thesis, the effects of vitamin D in multiple sclerosis have been investigated from both a clinical and immunological perspective. With that, the research in this thesis is translational research (from bench to bedside) [386] and in part already entered the process of valorisation.

- Taking immunological outcomes as a read-out, we saw that data on the *in vivo* effects of vitamin D in health and disease were heterogeneous in many aspects. A trend towards an anti-inflammatory role of vitamin D seemed to be present, but it was difficult to draw firm conclusions (reviewed in **chapter 1**)
- From a clinical point of view an important gap in our knowledge was the role of vitamin D in disease progression. Disease progression is one of the most important hallmarks of disability and has major impacts on the quality of life. We could demonstrate that vitamin D levels are predictors of disease activity and probably also the time to conversion to progressive disease, but only at the start of the disease and not later on, during the disease course (**chapter 2 and 3**).
- From the bench side view, we improved the technique to discover IL-10, one of the important cytokines in our body, in terms of immune regulation (**chapter 4**).
- From the bench to bedside view, we looked at the role of GM-CSF in human MS: GM-CSF^+ T cells were equally present in patients and controls, and were increased in CSF compared to blood. We discovered that the number of GM-CSF^+ T cells are probably not affected by vitamin D, but functionally they were regulated by regulatory T cells and vitamin D, the latter one being less effective in patients with MS than in healthy controls (**chapter 5**).
- In a RCT, already on our way to valorisation of vitamin D supplementation, we showed that high dose vitamin D supplementation is not able to promote immune cell balance, but that it is able to prevent further disturbance of the immune balance during the disease course in early MS (**chapter 6**)

The innovative character of our studies

With the results from our studies we can make some steps further in finding an answer to the "hype or hope" question. From our clinical studies we can make more clear what the target group of patients is, which will benefit most from (high dose) vitamin D supplementation. These are the patients at the start of their disease or patients or even healthy individuals in the pre-clinical phase of the disease. With our immunological studies on GM-CSF and vitamin D, we have aimed to translate findings from animal and *in vitro* research to *in vivo* effects in humans. The added value of the SOLARIUM study compared to previous studies was that this was a placebo controlled study with relevant power, and a high dose (14.000 IU/day) and long term (48 weeks) vitamin D_3 supplementation intervention. Furthermore, another point of interest is that we looked at the regulatory immune cell compartment and T cell compartment as a whole in this study, not focusing on a single cell or cytokine. [387]

Application, interaction and inspiration

Applicable science

The studies described in this thesis are able to contribute to the use of scientific knowledge in different ways.

First of all, they increase our understanding in the pathophysiology and the role of environmental factors in the disease multiple sclerosis and in auto-immunity. Furthermore, with our research on GM-CSF producing T cells, we added new information to the field, information that should be kept in mind when developing GM-CSF therapies in MS. [388]

Second, with regard to the vitamin D supplementation therapy, we showed that it can overcome a further imbalance in the immune system during the course of the disease. Of course, clinical outcomes have to confirm our findings, but if so, we have hints towards a narrow window of opportunity for vitamin D supplementation at the start of the disease and should further investigate the optimal dose. These recommendations should then be incorporated in guidelines for general practitioners and neurologists treating patients with auto-immune diseases like MS. With regard to high dose vitamin D supplementation two other options might be worthwhile to deliberate on. First, it might be worthwhile to investigate the effectiveness of high dose vitamin D supplementation in the pre-clinical phase, during childhood and adolescence in people sensitive to developing auto-immune diseases. This probability to develop an auto-immune disease should possibly take into account an individuals' genetic make-up, month of birth, place of birth, family history and ethnicity. Second, as already deliberated on in the general discussion of this thesis, it might be lucrative to think about *in vitro* treatment of autologous immune cells, for example T cells, with vitamin D and replacement of those cells in the human body. Hereby, the *in vivo* (compensatory) effects, as shown in our vitamin D supplementation study, might be circumvented and efficacy increased. [347]

Implementation by interaction and inspiration

Implementation of scientific knowledge is not only about "knowledge, skills and cash". It also includes more "soft skills" for example communication, cooperation and collaboration. [379] Our research is of course first of all most interesting for (future) patients with MS and their treating physicians. They should be informed about our research activities. Efforts have already been made via the website of the Academic MS Centre, via patient associations and via presentations at patient days. Our studies were published in (bio)medical journals and presented at national and international congresses to reach treating physicians and colleagues from different biomedical disciplines, like the neurology, immunology and vitamin D field. Future colleagues had the opportunity to learn about our research during lectures for students in the medical and biomedical field and for nurses, or by performing an internship in our group. The "7 UMC tour", a day organised to celebrate the 50 years birthday of the Dutch Society of Immunology in 2014, was an example of an opportunity we took to also inform the general public about our research.

If our immunological results in the SOLARIUM study will be confirmed by positive results of clinical outcomes in the SOLAR trial, it will become important to reach consensus if, when and how to prescribe high dose vitamin D supplementation to patients with MS and to incorporate these advices in national and international guidelines. To fasten the process of a possible implementation of GM-CSF therapy and vitamin D supplementation therapy, also the expertise of pharmaceutical companies and policy makers should be used for optimal valorisation. Pharmaceutical companies will have added value by their knowledge on implementation of drugs to the market and, especially if there are more clues pointing to preventive medicine, policy makers should get involved to make people aware of the sense and nonsense about vitamin D. Lastly, if *in vitro* treatment of T cells with vitamin D is promising enough to enter a clinical phase study, clinical immunologists should stay involved.
Apart from these hopes for the future there are also still some challenges to tackle: MS is a very heterogeneous disease, and our results are not that easy translatable to all MS patients. Furthermore, big challenges are there for (bio)medical research in general: how to deal with big datasets, how to increase reproducibility, how to objectively analyse data, how to make translation from animal to human more efficient [353, 354, 373, 374], how to build bridges between the different research areas [371, 372] and different professional groups in healthcare, how to make it possible that negative data get the same attention as positive data [375] and how to reduce waste and maximise efficiency of research sources? Some initiatives have already started (for example the REWARD (REduce research Waste And Reward Diligence) Campaign of the Lancet and the Dutch "Science in Transition" initiative that aims to introduce new checks and balances in the scientific system and inform layman about the decisions made [396, 397]), but we all have to think and work together on that. Only then valorisation of research as that described in this thesis will become easier and more efficient in the future.

Conclusion

Multiple sclerosis is a disabling disease, with much impact on individuals, but also on society. This thesis touches upon several of the most important research questions in this disease with a special attention to the role of vitamin D. Approached from a clinical and immunological perspective, this thesis already describes translational research. Further valorisation needs to be done by staying critical towards research methods and results of ourselves and of others and continuing the communication and collaboration with different disciplines, with some important challenges for the biomedical field ahead for the future.