Regulation of the stress-axis by vitamin D3 in subjects with multiple sclerosis; a double-blinded, randomized, placebo-controlled study

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The main aim of this study is to assess hypothesis A, and we will perform an exploratory analysis on hypothesis B.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON45180

Source
ToetsingOnline

Brief title
Vitamin D3 and the stress-axis in MS

Condition

- Autoimmune disorders
- Demyelinating disorders

Synonym
Multiple Sclerosis; MS

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht

Source(s) of monetary or material Support: Financiering vindt vanuit eigen middelen plaats;o.a. door financiering vanuit het Nationaal MS Fonds.

Intervention

Keyword: cortisol, HPA-axis, Multiple sclerosis, Vitamin D3

Outcome measures

Primary outcome

We assess primarily the effect of vitamin D3 supplementation with a dose of

4000 IU/day (100µg/ day) for 16 weeks on the cortisol day curve.

Secondary outcome

Furthermore, we assess the effect of the intervention on the slope of the

cortisol day curve, a dexamethason suppression test, the cortisone awakening

response, the CD4+ T cell cytokine profile and the HADS depression/ FSSS

fatigue score, and we assess descriptively to which extent vitamin D levels in

the serum are elevated, and assess whether the participant experience

side-effects.

Study description

Background summary

MS patients are at risk for developing depressive symptoms. Also, impaired vitamin D levels are associated with a higher risk of developing MS and with a more severe MS course. Our group observed a relationship between vitamin D status and the risk of developing depressive symptoms, suggesting an interaction between vitamin D and biological mechanisms affecting susceptibility to depression. Currently, we have two main hypotheses. Hypothesis A: Vitamin D regulates the hypothalamic stress axis in MS. Both MS patients and non-MS patients with a major depression have increased levels of circulating cortisol, due to hyper-reactivity of hypothalamic-pituitary-adrenal (HPA)-axis, also known as the stress axis. Previous research showed that vitamin D receptors in the brain are particularly expressed in the hypothalamus

and that vitamin D also may affect cortisolcorticotrophin releasing hormone (CRH)-positive cells. We postulate that vitamin D may regulate the release of CRH, and hereby is able to suppress the activity of the HPA-axis and protects MS patients for developing depressive symptoms in MS . Hypothesis B: Vitamin D affects T cell cytokine profile and hereby the odds of developing depression. In our previous studies, we showed that the cytokine profile of peripheral blood CD4+ T cells correlates with vitamin D status in MS patients and that vitamin D may promote T cell homeostasis in MS. Since both MS patients and non-MS patients with a major depression display increased circulating levels of pro-inflammatory cytokines and anti-depressants reduce those cytokines, an inflammatory component may contribute to the development or presence of depressive symptoms in MS , with whom vitamin D may interfere.

Study objective

The main aim of this study is to assess hypothesis A, and we will perform an exploratory analysis on hypothesis B.

Study design

This will be a randomized, double-blinded, placebo-controlled clinical study.

Intervention

Patients have to take 100ug vitamine D3 solution a day for a period of 16 weeks.

Study burden and risks

Patients have to take the vitamin D solution every day and have to visit the hospital 3 times for giving urine and blood samples. Also they have to collect several salivasamples at the start and the end of the study, covering 4 full days.
An elevation of serum calcium levels (hypercalcemia) has occasionally been described in patients supplemented with high doses of vitamin D. A severe hypercalcemia can give rise to complications as heart- and kidney faillure. However, the amount of vitamin D that we supplement, de frequency of monitoring and the exclusion of potential highrisk groups reduce this risk significantly.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- relapsing remitting multiple sclerosis (revised McDonald criteria 2005)
- female
- age >18 years
- premenopausal
- At start of study > 6 weeks in clinical remission of disease
- use of no immune-modulating treatments or the currently registered firstline immune modulating therapies (including Interferon-beta (1a or 1b), glatiramer acetate, dimethylfumarate, teriflunomide) or second-line immune modulating therapies (incl. fingolimod (Gilenya) and natalizumab (Tysabri)).

Exclusion criteria

• Any contraindication to vitamin D according to Summary of Product Characteristics: Hypercalcaemia, hypervitaminosis D, nephrolithiasis, diseases or conditions resulting in hypercalcaemia and/or hypercalciuria (incl. primary hyperparathyroidism), severe renal impairment.
• Use of dexamethasone or other systemic glucocorticosteroids <2 months prior to first study

visit
• Supplementation of >=1000 IU/d (25µg) vitamin D2 or D3
• Medical history of disturbed vitamin D/ calcium metabolism other than low intake
• Present clinical (major)depression
• Present treatment with anti-depressants, benzodiazepines, or neuroleptics.
• Treatment with high-dose dexamethasone for MS exacerbation during study.
• Pregnancy or the intention to become pregnant during the study period.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-10-2014
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Vigantol Oil
Generic name:	Colecalciferol

Ethics review

Approved WMO

Date:	18-11-2013
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	08-05-2014
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	19-08-2015
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	24-03-2016
Application type:	Amendment
Review commission:	METC Atrium-Orbis-Zuyd

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-000728-97-NL
ClinicalTrials.gov	NCT02096133
CCMO	NL45995.096.14