Medical Hypotheses xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Will vitamin D supplementation ameliorate diseases characterized by chronic inflammation and fatigue?

Anna Dorothea Hoeck [a,*], Martin L. Pall [b]

[a] Mariawald str. 750935, Cologne, Germany
[b] The Tenth Paradigm Research Group and School of Molecular Biosciences (WSU)638, 41[st], Portland and OR 97232-3312, NE, USA

ARTICLE INFO

Article history:
Received 9 April 2010
Accepted 30 September 2010
Available online xxxx

SUMMARY

Chronic NF-κB activation has been supposed as a key event in chronic fatigue syndrome (CFS) and many other better-defined pro-inflammatory diseases. Knowledge about the impact of deficiency vitamin D on chronic NF-κB activation could open a new disease approach.

Whereas NF-κB activation leads at first to a pro-inflammatory immune response, later on a vitamin D-dependent anti-inflammatory response ensues. Binding of the active vitamin D metabolite $1,25(OH)_2D_3$ to vitamin D receptor (VDR) yields a transcription factor which represses NF-κB activation, and additionally modulates and down-regulates adaptive, but enhances innate immune responses, and improves redox balance, thus counterbalancing inflammation on multiple levels. However, this built-in late counterbalance against inflammation works only when stores of calcium and $25(OH)D_3$ are abundant.

Therefore a connection between lowered vitamin D-metabolism and persistent NF-κB activation, augmented nitrosative-oxidative stress, redox imbalance, chronic inflammation, and concomitant fatigue can be postulated.

In order to confirm this hypothesis, randomized controlled clinical studies about the clinical effects of supplementation of calcium and vitamin D_3 would be necessary in diseases characterized by persistent NF-κB activation and chronic inflammation and fatigue.

Initial stress response is pro-inflammatory and self-amplifying

In chronic inflammatory illnesses, like for instance rheumatoid arthritis, chronic fatigue is a well accepted symptom accompanying or even preceding clinical relapse. Well known causes inducing fatigue are pro-inflammatory cytokines and lowered ATP pool (energy loss). Meanwhile, chronic inflammatory diseases, but also chronic fatigue syndrome (CFS) and related disorders, are presumed to be connected with persistent activation of nuclear factor-kappa B (NF-κB) resulting in augmented nitrosative-oxidative stress, lowered ATP pools, and chronic inflammation [1–3].

On the other hand, a stress-induced vicious up-regulation of nitric oxide/peroxynitrite ($NO/ONOO^-$) cycle, as a local event, and discussed extensively elsewhere, is presumed to lead in a multi-step manner to several diseases, also named multi-system illnesses [4–12].

However, NF-κB activation and augmented nitrosative-oxidative stress are key events in this cycle, as well. Therefore NF-κB activation might be a central topic of this disease mechanism.

NF-κB activation is an essential defence response mechanism in innate immune system [13–15] altering protein synthesis [16], gene expression before, during and after transcription [3,16–18], as well as growth, differentiation, and apoptosis [3,19]. NF-κB activation induces the production of high levels of reactive oxygen species (ROS), like superoxide ($O^{\cdot}O^-$), on the one hand, and of nitric oxide ($NO^{\cdot}$), at the other hand, with resulting generation of peroxynitrite ($ONOO^-$), thus leading to altered cellular structures and functions [10,20–28]. In particular, metabolic consequences will ensue like derangement of citric acid cycle and oxidative phosphorylation, resulting in lowered ATP [10,25,26] and NADH/NAD redox pool [10,23–26].

It is important to realize that NF-κB activation possesses an inherent self-amplifying potency by induction of interferon-γ (IFN-γ), pro-inflammatory cytokines like interleukin-1-beta (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-α), and inducible NO synthase (iNOS) [28,29], with the net result of overproduction of ROS [29–34] which activate NF-κB once more. However, this is not the only positive back loop. INF-γ, IL-2, and TNF-α activate NF-κB directly [29], creating another feed-forward loop. Furthermore, ROS damage ion channels, in particular calcium pumps. By this way free intracellular calcium (Ca^{2+}_{ic}) levels become elevated

* Corresponding author. Tel.: +49 221 466650.
E-mail address: ad.hoeck@t-online.de (A.D. Hoeck).

0306-9877/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2010.09.032

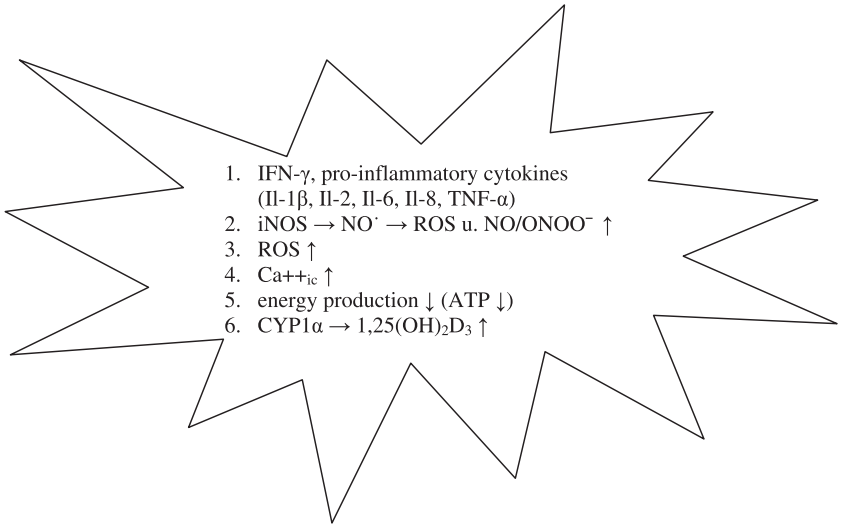

Fig. 1. NF-κB activation induces a burst of stress responses [23,28,29,38]. Abbreviations: $1,25(OH)_2D_3$: 1,25-dihydroxyvitamin D_3, ATP: adenosine triphosphate, Ca^{2+}_{ic}: free intracellular calcium, CYP1α: 25-hydroxyvitamin D-1-alpha-hydroxylase, IFN-γ: interferon gamma (type II interferon), ILl-1β: interleukin-beta 1, IL-2: interleukin-2, IL-6: interleukin-6, IL-8: interleukin-8, iNOS: inducible NO-synthase, NF-κB: nuclear factor-kappa B, NO: nitric oxide, NO/ONOO: peroxinitrite, ROS: reactive oxygen species, TNF-α: tumor necrosis factor-alpha.

[29–31] which, like ROS, are able to induce a new round of NF-κB activation [29].

This inherent trend towards initial augmentation of pro-inflammatory stress response might play an essential pathogenic role in chronic inflammatory and auto-immune diseases if no effective counterbalance of NF-κB activation ensues in late stress response (Fig. 1). Exactly this scenario of not properly opposed pro-inflammatory immune and stress response, with chronic elevation of Ca^{2+}_{ic}, extensive production of ROS, and redox imbalance is described in chronic calcium and vitamin D deficiency [35–42].

The pleiotropic actions of vitamin D in metabolism

Vitamin D comprises vitamin D_3 and vitamin D_2. Vitamin D, which may come either from suntanned skin, diet or supplements, is synthesized in the liver to 25-hydroxy-cholecalciferol [25(OH)D3)] which is activated by the enzyme 25-hydroxyvitamin D-1 α-hydroxylase (CYP27B1) to become 1,25-dihydroxyvitamin D_3 [1,25(OH)2D3], designated as "activated" vitamin D_3 [23,45,46].

A well known activation process from $25OHD_3$ to $1,25(OH)_2D_3$ is mediated in the tubular cells of the kidney in a calcium dependent manner by parathormone (PTH), and serves to control extra-cellular calcium levels [23,43–45,47]. A calcium independent, vitamin D_3 stores dependent activation occurs in more than 10 tissues in order to ensure specific cellular needs, for instance control of cell growth, proliferation, differentiation, or apoptosis [37,43–45]. $1,25(OH)_2D_3$ binds to a receptor protein, named vitamin D receptor (VDR). This complex acts as transcription factor and regulates the expression of a host of different genes [46–53]. Besides the genomic actions of $1,25(OH)_2D_3$, non-genomic actions operate on several signaling pathways, described elsewhere [43,47,49–50]. Genomic and non-genomic actions are interrelated by substantial cross-talk [43,50–52]. These pleiotropic actions are supposed to influence general health considerably. However, this paper concentrates on effects of $1,25(OH)_2D_3$ on regulation of NF-κB, immune functions, Ca^{2+}_{ic}, and redox balance, which are all strongly linked to stress pathways and $NO/ONOO^-$ cycle.

$1,25(OH)_2D_3$ enhances early and calms down late stress response

Cell stress of any kind, like heat, inflammation, oxidative stress, interferon (IFN), and the active metabolite $1,25(OH)_2D_3$ itself, are able to induce heat shock 70 (Hsp-70)-like proteins, called intracellular vitamin D-binding proteins (IDBP). They belong to a large family of ATP binding stress proteins acting as ATPases and chaperones [53]. Preferentially $25(OH)D_3$ has a great affinity to bind to these proteins, but $1,25(OH)_2D_3$ can also bind [53,54]. The complex of Hsp-70 like proteins with $25OHD_3$ or $1,25(OH)_2D_3$ interacts with toll-like receptor 2 (TLR2) leading to activation of NF-κB as part of an overall defence mechanism against cell stress [53–55]. Thus, vitamin D enhances early stress response [53–58].

However, activation of NF-κB induces as well gene expression of CYP27B1 [34–40,53,56–58], thus promoting augmented synthesis of $1,25(OH)_2D_3$ (Fig. 2) which inhibits gene expression of multiple products of NF-κB activation, like IFN-γ, IL-2, IL-6, iNOS, and TNF-α [40,59–63], and down-regulates NF-κB activation directly by inhibition of several NF-κB-related proteins [39,42,53], and more indirectly via numerous further mechanisms, and in multiple cells [38–43,49,53,47–55,59–63]. The net result is potent inhibition of responses that will otherwise limit chronic inflammation. Thus, opposite to the early stress response, $1,25(OH)_2D_3$ is able to suppress the late pro-inflammatory stress responses.

Regardless of the mentioned inhibitory effect on iNOS expression, there is coupled gene expression of the iNOS gene and $1,25(OH)_2D_3$ synthesis in activated macrophages (Mø), dendritic cells (DCs) and T-cells [38,42,56–59]. This may lead to very high levels of $1,25(OH)_2D_3$, even spilling over into blood [56,57]. This coupling economizes cellular redox balance in case of cell stress, as moderate amounts of NO, instead of NADPH, may be able to act as electron donator for the synthesis from $25(OH)D_3$ to $1,25(OH)_2D_3$, thus saving the stores of NADPH [53,57] which contributes to anti-inflammation. On the contrary, high concentrations of NO block the enzymatic activity of CYP27B1, thus lowering the synthesis of $1,25(OH)_2D_3$ in this condition, now contributing to pro-inflammation [57].

$1,25(OH)_2D_3$ induces immune regulation and tolerance

$1,25(OH)_2D_3$ counteracts inflammation through many indirect immune mechanisms as well. For instance, it represses interleukin-12 (Il-12) in macrophages [39,47,53,56,59,62] and myeloid dendritic cells (mDCs) [39,41,42,47,63] resulting in diminished

Please cite this article in press as: Hoeck AD, Pall ML. Will vitamin D supplementation ameliorate diseases characterized by chronic inflammation and fatigue? Med Hypotheses (2010), doi:10.1016/j.mehy.2010.09.032

EARLY STRESS RESPONSE IS A POSITIVE INFLAMMATORY AMPLIFICATION LOOP

heat, stress, $1,25(OH)_2D_3$ → hsp-70 like proteins (IDBP) ↑ → $1,25(OH)_2D_3$/IDBP complex activates TLR2

→ signal cascade → ACTIVATION of NF-κB → INFγ, IL-2, TNF α, LPS, $Ca{+}{+}_{ic}$ ↑, ROS ↑

→ new round of ACTIVATION of NF-κB → disposition to vicious local NO/$ONOO^-$ cycle

IN CASE OF VITAMIN D AND CALCIUM REPLETION,
LATE STRESS RESPONSE IS ABLE TO CREATE NEGATIVE FEED BACK LOOPS AGAINST INFLAMMATION

NF-κB → iNOS ↑ and CYP1α ↑ → NO ↑ and $1,25(OH)_2D_3$ ↑

[$NO^{\cdot}$ serves as electron donator for synthesis of $1,25(OH)_2D_3$ (NADPH economy)]

$1,25(OH)_2D_3$ INHIBITS many NF-κB proteins (p105/p50, c-Rel, Rel-B) and products (IFN-γ, IL-2, IL-6, IL-12, iNOS, TNF-α) and

INHIBITS more indirectly activation of NF-κB, on several levels and in many cells

Fig. 2. Abbreviations: ATP: adenosine triphosphate, $1,25OH_2D_3$: activated vitamin D_3 metabolite (1,25-dihydroxyvitamin D_3), $25OHD_3$: provitamin D_3 metabolite (25-hydroxycholecalciferol), $Ca^{2+}{}_{ic}$: free intracellular calcium, CYP1α: (CYP27b) 25-hydoxyvitamin D_3-1-alpha-hydroxylase, hsp70: heat-shock-protein 70, IFN-γ: interferon-gamma, IL-2: interleukin 2, IL-6: interleukin-6, iNOS: inducible NO-synthase, LPS: lipopolysaccharide, NADPH: reduced nicotine-adenine-dinucleotide-phosphate, NF-κB: nuclear factor-kappa B, NO: nitric oxide, NO/ONOO: peroxynitrite, ROS: reactive oxygen species, TLR2: Toll-like-receptor 2, TNF-α: tumor necrosis factor-alpha.

immune maturation with subsequent inhibition of auto-immune Th1 responses. As well, $1,25(OH)_2D_3$ mitigates immune response in antigen presenting and T-cells by differentially influencing gene expression of ligands, like cytokines and chemokines [38–40], multiple immune receptors [38,62], and co-stimulatory membrane proteins, MHC II receptors, and other immune-regulatory proteins [38–42,59,62] (Table 1). Furthermore, $1,25(OH)_2D_3$ inhibits in T-cells the expression of Fas-ligand (CD95L) [38] which is a co-stimulatory signal for immune maturation and polarization in $CD8^+$ cells, Th1 cells and mDCs [38]. The result is enhanced development of less immune-matured and hence more immune-naïve regulatory $CD24^+CD25^+$-T-lymphocytes (T_{reg}) [39–42,62,63].

Table 1
$1,25(OH)_2D_3$ INDUCES IMMUNE REGULATION AND IMMUNE TOLERANCE [38–40,42,53,62].

NF-κB ↓ (m-DCs, $CD4^+$-T-cells) → iNOS ↓, NO ↓ → inflammation ↓
NF-κB ↓ (APC, m-DCs) → IL-12 ↓ , maturation of m-DCs and T-cells ↓, → T_{reg} → immune tolerance↑
NF-κB ↓ (APC, m-DCs) → IL-12 ↓ , Th1-cells ↓ (number and function), co-stimulatory molecules CD40, CD80, CD86 ↓ (m-DCs) → enhancement of T_{reg}
Adhesion molecules (CD54) ↓ (m-DCs) → enhancement of T_{reg}
MHC-II-antigen receptors ↓ (m-DCs) → enhancement of T_{reg}
Inhibitory membrane protein ILT3 ↑ (APC) → enhancement of T_{reg}
CCR 4, CCR5, CCR 8, CCR10 ↑ → enhancement of T_{reg}
CCL22 ↑, CCL17 ↓ (APC) → enhanced recruitment of T_{reg}
IL-10 ↑ (m-DCs) (an anti-inflammatory cytokine) → inflammation ↓
NK- und CTL-activity in cognate immune system ↓
GM-CFS ↓ (m-DCs) → monocytes ↓
IFN-γ ↓, TNFα ↓, IL-1 ↓, IL-2 ↓, IL-6 ↓, IL-8 ↓, IL-12 ↓, Il-17 ↓, IL-23 ↓
COX-2 ↓ in Mø

Abbreviations: APC, antigen presenting cells, CCL22, anti-inflammatory chemokine; CCL17, pro-inflammatory chemokine; CCR 4, CCR5, CCR 8, CCR10, chemokine receptors; COX-2, cyclooxygenase-2; CTL, cytotoxic T-cells, m-DCs, myeloid dendritic cells; IFN-γ, interferon gamma; IL-1, interleukin-1; IL-2, interleukin-2; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL-12, interleukin-12; IL-17, interleukin 17; IL-23, interleukin 23; iNOS, inducible NO-synthase; Mø, macrophage; NF-κB, nuclear factor-kappa B; NK, natural killer cells"; NO, nitric oxide; Th1-cells, T-helper cells type 1; TNF-α, tumor necrosis factor-alpha.

$1,25(OH)_2D_3$ supports innate defence against microbes

$1,25(OH)_2D_3$ helps innate immune system in first line defence against microbial invasion [38,44,53–58,60,64] (Table 2). $1,25(OH)_2D_3$ enhances monocyte maturation into macrophages [38,53,56,57], as well as macrophage antigen uptake by antigen presenting cells, antigen cell trafficking [38,53,56,57], expression of interleukin-1β (IL-1 β) [53,56,57], TNF-α [38,53,56,57], and NADPH-oxidase [38,39,53,56,64], thus augmenting pathogen killing ability and hydrogen peroxide (H_2O_2) production. Furthermore, $1,25(OH)_2D_3$ enhances the synthesis of cathelicidin, an agent with inherent anti-microbial potency against viral, bacterial and fungal invasion, secreted locally in antigen presenting cells and keratinocytes [40,54,55]. As all these mechanisms serve as appropriate tools to shut down inflammation as early as possible, they contribute to NF-κB counterbalance.

$1,25(OH)_2D_3$ is essential for redox balance

$1,25(OH)_2D_3$ can act as a pro-oxidant in appropriate cases [22], but also as a potent anti-oxidant [22,47] (Table 3). Like cholesterol, $1,25(OH)_2D_3$ is able to reduce the fluidity of the cell membrane and to prevent iron-dependent lipid peroxidation [65,66]. It increases

Table 2
$1,25(OH)_2D_3$ SUPPORTS FIRST LINE IMMUNE DEFENCE IN INNATE IMMUNE SYSTEM.

maturation of monocyte to macrophage ↑ [42]
MCP-1 ↑, MIP-1α ↑, MIP-1β ↑, CSF-1 ↑ (Mø) [42]
Antigen uptake ↑ (Mø) [38,39]
IL-β1 ↑, TNF-α ↑, NADPH-oxidase ↑, H_2O_2 ↑ (Mø) [53,64]
Cell trafficking of APCs↑ [38,39,53]
cathelicidin ↑ (APCs, keratinocytes) [40,54,55]

Abbreviations: $1,25OH_2D_3$, the activated vitamin D_3 metabolite 1,25-dihydroxyvitamin D_3; APC, antigen presenting cells; DCs, dendritic cells; H_2O_2, dihydrogen superoxide; IL-12, interleukin-12; IL-β1, interleukin beta 1, Mø; macrophage NADPH-oxidase; nicotine-adenine-dinucleotide-phosphate-hydrogen-oxidase; NF-κB, nuclear factor-kappa B; TNF-α, tumor necrosis factor-alpha.

Please cite this article in press as: Hoeck AD, Pall ML. Will vitamin D supplementation ameliorate diseases characterized by chronic inflammation and fatigue? Med Hypotheses (2010), doi:10.1016/j.mehy.2010.09.032

Table 3
VITAMIN D_3 ENHANCES REDOX BALANCE.

Vitamin D suppresses oxidative stress:
Reduction of iron-dependent lipid oxidation of cell membranes [65,66]
Activity of γ-GT increased [22,66]
Enhancement of synthesis of reduced glutathione [65–67]
Induction of GPX [65]
Induction of Mn-SOD [65]
Induction of metallothioneins [68]
Vitamin D suppresses reductive stress:
Enhancement of G6PD activity [65]
Lowering GR activity [47,65]

Abbreviations: γGT, gamma-glutamyl transpeptidase; G6PD, glucose-6-phosphate dehydrogenase; GPX, glutathione peroxidase; GR, glutathione reductase; Mn-SOD, manganese dependent superoxide dismutase.

the activity of gamma-glutamyl transpeptidase (γGT) [22,66], supports glutathione synthesis [65–67], induces glutathione peroxidase (GPX) [65], and manganese dependent superoxide dismutase (Mn-SOD) [65]. Furthermore, $1,25(OH)_2D_3$ induces the production of thiol-containing and metal-binding metallothioneins [68,69], thus preventing metal derived oxidative stress. By enhancing activity of glucose-6-phosphate-dehydrogenase (G6PD) [47,65] $1,25(OH)_2D_3$ is able to act also against oxidative stress. All these redox balancing abilities serve as another contribution to down-regulation of NF-κB activation.

However, $1,25(OH)_2D_3$ is able as well to lower glutathione reductase with a potentially pro-oxidant effect [47,65]. But being relatively modest and being found with all of the anti-oxidant responses, it is not likely to be a major influence.

Discussion

Calcium and vitamin D deficiency/insufficiency are nowadays "everyday" conditions in western world due to either living beyond the 40th degree of latitude, and/or frequent indoor working, and/or use of high protecting sun cream, for instance. Bone and connective tissue alteration, culminating in rickets [37], muscle weakness, wide spread pains [35–37], immune dysfunctions [37,54,55], and otherwise unexplainable chronic fatigue combined with functional disorders are meanwhile described as vitamin D dependent syndromes [35–37,75–77].

As long as $25OHD_3$ is abundant, local production of $1,25(OH)_2D_3$ will occur according to special cellular needs [22,37,45]. However, in case of low stores of $25(OH)D_3$, local production in tissues becomes diminished which deranges tissue homeostasis [22,37,45], generating high ROS and NO production especially in highly metabolically active body regions [21,22,27,43,46,47,69].

Whole body calcium deficiency is supposed to result from long-standing vitamin D deficiency, as levels of $25(OH)D_3$ lower than 40 ng/ml (100 nMol/L) are said to compromise adequate calcium absorption [43,71,73,74]. Due to calcium deficiency, compensatory mechanisms like PTH secretion, for instance, and other bone resolving mechanisms might contribute to pro-inflammation, even when vitamin D stores become replenished [70–78], and might explain why calcium optimizes vitamin D supplementation substantially [43,69,71,74].

Additionally, it should be of interest that a rise of PTH in the wake of calcium deficiency will provoke enhanced CYP27B1 activity, thus leading to increased turnover of $25(OH)D_3$ which means more rapid reduction of actual vitamin D stores [43,70–78].

In summary, raising $1,25(OH)_2D_3$ levels subsequent to an initial inflammatory or unspecific stress response can act to lower pro-inflammatory immune responses by twelve mechanisms:

(1) Down-regulating NF-kappa B activity
(2) Lowering iNOS induction
(3) Lowering IL-6
(4) Lowering IL-2
(5) Lowering IFN gamma
(6) Lowering IL-12 synthesis
(7) Increased G6PD
(8) Increased metallothioneine synthesis
(9) Increased Mn-SOD
(10) Increased reduced glutathione synthesis
(11) Increased gamma-glutamyl transpeptidase
(12) Lowering iron-dependent lipid peroxidation

The depletion of vitamin D pools in the tissues that can be used to elevate local $1,25(OH)_2D_3$ in response to local inflammation may be a very important limiting factor in preventing or reversing chronic inflammation. Therefore vitamin D supplementation is likely to be important both as a preventive agent or treatment of many chronic inflammatory diseases, whether these are caused by the NO/ONOO-cycle, auto-immune response or by other mechanisms.

Improvement of inflammatory disease course has been already described [77], yet no studies in case of full-blown CFS and related diseases have been done until now. With respect to recent papers connecting chronic fatigue syndrome with a possible opportunistic pathogen [79], and chronic NF-κB activation with reactivation of latent and opportunistic pathogens [80–82], future controlled, randomized, and double blind studies seem to be reasonable. Clinical effectiveness could be compared with respect to different calcium and vitamin D compounds and dosages.

Conflict of interest

The authors declared that no conflict of interest is existing.

References

[1] Maes M, Mihaylova I, Bosmans E. Not in the mind of neurasthenic lazybones but in the cell nucleus: patients with chronic fatigue syndrome have increased production of nuclear factor kappa beta. Neuro Endocrinol Lett 2007;28(4):456–62.
[2] Frémont M, Vaeyens F, Herst C, De Meirleir K, Englebienne P. Antiviral pathway deregulation of chronic fatigue syndrome induces nitric oxide production in immune cells that precludes a resolution of the inflammatory response. J Chronic fatigue Syndr 2006;13:17–28.
[3] Hovanessian AG. On the discovery of interferon-inducible, double-stranded RNA activated enzymes: the 2'-5'-Oligoadenylate synthetases and the protein kinase PKR. Cytokine Growth Factor Rev 2007;18:351–61.
[4] Pall ML. Elevated, sustained peroxynitrite levels as the cause of chronic fatigue syndrome. Med Hypotheses 2000;1:115–25.
[5] Pall ML. : Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxinitrite. Med Hypotheses 2001;57:139–45.
[6] Pall ML. NMDA sensitization and stimulation by peroxynitrite, nitric oxide and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity. FASEB J 2002;16:1407–17.
[7] Pall ML. Elevated nitric oxide/peroxynitrite theory of multiple chemical sensitivity: central role of N-methyl-D-aspartate receptors in the sensitivity mechanism. Environ Health Perspect 2003;111:1461–4.
[8] Pall ML, Anderson JH. The vanilloid receptor as a putative target of diverse chemicals in multiple chemical sensitivity. Arch Environ Health 2004;59:363–75.
[9] Pall ML. Nitric oxide and the etiology of chronic fatigue syndrome: Giving credit where credit is due. Med Hypotheses 2005;65(3):631–3.
[10] Pall ML. Explaining unexplained illnesses Disease paradigm for chronic fatigue syndrome, multiple chemical sensitivity, fibromyalgia, post-traumatic stress disorder, gulf war syndrome, and others. New York: Harrington Park Press; 2006.
[11] Pall ML. Nitric oxide synthase partial uncoupling as a key switching mechanism for the NO/ONOO-cycle. Med Hyotheses 2007;69(4):821–5.
[12] Maes M, Mihaylova I, Kubera M, Bosmans E. Not in the mind but in the cell: increased production of cyclooxygenase-2 and inducible NO synthase in chronic fatigue syndrome. Neuro Endocrinol Lett 2007;28(4):463–9.

Please cite this article in press as: Hoeck AD, Pall ML. Will vitamin D supplementation ameliorate diseases characterized by chronic inflammation and fatigue? Med Hypotheses (2010), doi:10.1016/j.mehy.2010.09.032

[13] Hiscott J. Convergence of the NF-κB and IRF pathways in the regulation of the innate antiviral response. Cytokine Growth Factor Rev 2007;18:483–90.
[14] Stark GR. How cells respond to the interferons revisited: From early history to current complexity. Cytokine Growth Factor Rev 2007;18:419–23.
[15] Gantier MP, Williams BRG. The response of mammalian cells to double-stranded RNA. Cytokine Growth Factor Rev 2007;18:363–71.
[16] Rana TM. Illuminating the silence. understanding the structure and function of small RNAs. Nature Rev Mol Cell Biol 2007;8:23–36.
[17] Bisbal C, Silverman RH. Diverse functions of RNase L and implications in pathology. Biochimie 2007;89:789–98.
[18] Silverman RH, Williams BRG. Translational control perks up. Nature 1999;397:208–11.
[19] Williams BRG. Role of the double–stranded RNA-activated protein-kinase (PKR) in cell regulation. Biochem Soc Trans 1997;25:509–13.
[20] Keefer LK. Nitric oxide in biochemistry and drug design. In: Meyers RA, editor. Molecular Biology and Biotechnology. New York: VCH Publishers; 1995. p. 579–601.
[21] Kröncke KD, Klotz LO, Suschek CV, Sies H. Comparing nitrosative versus oxidative stress toward zinc finger-dependent transcription Unique role for NO. J Biol Chem 2002;277:13294–301.
[22] Koren R, Ravid A. Vitamin D and the cellular response to oxidative stress. In: Feldman D, edtior. Vitamin D, Amsterdam: Elsevier Academic Press, Inc; 2005. p. 761-770.
[23] Löffler G, Petrides PE, Heinrich PC, eds. Biochemie und Pathobiochemie. Heidelberg: Springer Verlag 2007.
[24] Pollard TD, Earnshaw WC. Second messengers. In: Cell Biology. Pollard TD, Earnshaw WC, eds. Philadelphia: Elsevier 2004.
[25] Popovic Z, Templeton DM. Inhibition of an iron responsive element/iron regulatory protein-1 complex by ATP binding and hydrolysis. FEBS J 2007;274:3108–19.
[26] Tórtora V, Quijano C, Freeman B, Radi R, Castro L. Mitochondrial aconitase reaction with nitric oxide, S-nitrosoglutathione, and peroxynitrite: mechanisms and relative contributions to aconitase inactivation. Free Radic Biol Med 2007;42:1075–88.
[27] Daynes RA, Jones DC. Emerging roles of PPARS in inflammation and immunity. Nature Rev Immunol 2002;2:748–59.
[28] Lewis RS. Calcium oscillations in T-cells: mechanisms and consequences for gene expression. Biochem Soc Trans 2003;31:925–9.
[29] Mattson MP. Free radicals, calcium, and the synaptic plasticity-cell death continuum; emerging roles of the transcription factor NF-kB. Int Rev Neurobiol 1998;42:103–68.
[30] Choudhary G, Dudley Jr SC. Heart failure, oxidative stress, and ion channel modulation. Congest Heart Fail 2002;8(3):148–55.
[31] Grover AK, Kwan CY, Samson SE. Effects of peroxynitrite on sarco/endoplasmic reticulum Ca^{2+} pump isoforms SERCA2b and SERCA3a. Am J Physiol Cell Physiol 2003;285:C1537–43.
[32] Asehnoune K, Strassheim D, Mitra S, Kim JY, Abraham E. Involvement of reactive oxygen species in Toll-Like receptor 4-dependent activation of NF-kB. J Immunol 2004;172:2522–9.
[33] Malathi K, Paranjape JM, Bulanova E, et al. A transcriptional signaling pathway in the IFN system mediated by 2', 5'-oligoadenylate activation of RNase L. Proc Natl Acad Sci USA 2005;102:14533–8.
[34] De Meirleir K, Bisbal C, Camine I, et al. A 37 kDa 2–5A binding protein as a potential biochemical marker for chronic fatigue syndrome. Am J Med 2000;108:99–105.
[35] Boland RL. Vitamin D and muscle. In: Feldman D, editor. Vitamin D. Amsterdam: Elsevier Academic Press 2005; 883-897.
[36] Glerup H, Eriksen EF. Muscles and falls. In: Feldman D, editor. Vitamin D. Amsterdam: Elsevier Academic Press 2005; 1805-1820.
[37] Holick FM. Vitamin D. N Engl J Med 2007;357:266–81.
[38] Adorini L. Regulation of immune responses by vitamin D receptor ligands. In: Feldman D, edtior. Vitamin D. Amsterdam: Elsevier Academic Press 2005; 631-648.
[39] Adorini L. Intervention in autoimmunity: The potential of vitamin D receptor agonists. Cell Immunol 2005;233:115–24.
[40] Adorini L, Amuchastegui S, Corsiero E, Laverny G, Le Meur Th, Penna G. Vitamin D receptor analogs as anti-inflammatory agents. Exp Rev Clin Immunol 2007;3(4):477–89.
[41] Griffin MD, Lutz W, Phan VA, Bachman LA, McKean DJ, Kumar R. Dendritic cell modulation by 1α.25 dihydroxyvitamin D_3 and its analogs: A vitamin D receptor-dependent pathway that promotes a persistent state of immaturity in vitro and in vivo. Proc Natl Sci USA 2001;98(12):6800–5.
[42] Griffin MD, Xing N, Kumar R. Vitamin D and its analogs as regulators of immune activation and antigen presentation. Annu Rev Nutr 2003;23: 117–45.
[43] Fleet JC. Molecular regulation of calcium metabolism. In: Weaver CM, Heaney RP, editor. Calcium in Human Health. Totowa, New Jersey: Humana Press 2006; 163-189.
[44] Lou YR, Tuohimaa P. Is Calcidiol an active hormone? In: Stolzt VD, editor New Topics in Vitamin D Research New York: Nova Science Publishers 2006: 1-28.
[45] Vieth R. The pharmacology of vitamin D, including fortification strategies. In: Feldman D, edtior. Vitamin D. Amsterdam: Elsevier Academic Press 2005; 995-1015.
[46] Carlberg C, Dunlop TW, Frank C, Väisänen S. Molecular basis of the diversity of vitamin D target genes. In: Feldman D, edtior. Vitamin D. Amsterdam: Elsevier Academic Press 2005; 313-325.
[47] Chatterjee M. Vitamin D and genomic stability. Mutat. Res. 2001;475:69–88.
[48] Farach-Carson MC, Bergh JJ. Effects of 1,25-Dihydroxyvitamin D_3 on voltage-sensitive calcium channels in the vitamin D endocrine System. In: Feldman D, edtior. Vitamin D. Amsterdam, Elsevier Academic Press 2005; 751-60.
[49] Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. Endocr Rev 2005;26:662–87.
[50] Norman AW.1α,25$(OH)_2$-vitamin D_3 mediated rapid and genomic responses are dependent upon critical structure-function relationships for both the ligand and the receptor(s). In: Feldman D, edtior. Vitamin D. Amsterdam: Elsevier Academic Press 2005; 381-407.
[51] Whitfield GK, Jurutka PW, Haussler CA. Nuclear vitamin D receptor: structure-function, molecular control of gene transcription, and novel bioactions. In: Feldman D, edtior. Vitamin D, Amsterdam: Elsevier Academic Press 2005; 219-261.
[52] Boyan BD, Schwartz Z. Cartilage and vitamin D: Genomic and nongenomic regulation by 1,25$(OH)_2D_3$ and 24,25 $(OH)_2D_3$. In: Feldman D, edtior. Vitamin D, Amsterdam: Elsevier Academic Press 2005; 575-597.
[53] Hewison M, Adams JS. Extra-renal 1α−hydroxylase activity and human disease. In: Feldman D, edtior. Vitamin D, Amsterdam: Elsevier Academic Press 2005; 1379-1400.
[54] Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770–3.
[55] Schauber J, Dorschner RA, Coda AB, et al. Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. J Clin Invest 2007;117:803–11.
[56] Adams JS, Ren SY, Arbelle J, Shany S, Gacad MA. Coordinate regulation of nitric oxide and 1, 25-dihydroxyvitamin D production in the avian myelomonocytic cell line HD-11. Endocrinology 1995;136:2262–9.
[57] Adams JS, Ren SY. Autoregulation of 1, 25-dihydroxyvitamin D synthesis in macrophage mitochondria by nitric oxide. Endocrinology 1996;137:4514–7.
[58] Pryke AM, Duggan C, White CP, et al. Tumor necrosis factor-alpha induces vitamin D-1-hydroxylase activity in normal alveolar macrophages. J Cell Physiol 1990;142:652–6.
[59] D'Ambrosio D, Cippitelli M, Cocciolo MG, et al. Inhibition of IL-12 production by 1, 25-dihydroxyvitamin D3. Involvement of NF-kappa B down-regulation in transcriptional repression of the p40 gene. J Clin Invest 1998;101:252–62.
[60] Chang JM, Kuo MC, Kuo HT, et al. 1-α, 25-Dihydroxyvitamin D3 regulates inducible nitric oxide synthase messenger RNA expression and nitric oxide release in macrophage like RAW 264.7 cells. J Lab Clin Med 2004;143:14–22.
[61] Lefebvre d'Hellencourt C, Montero-Menei CN, Bernard R, Couez D. Vitamin D inhibits pro-inflammatory cytokines and nitric oxide production in the EOC13 microglial cell line. J Neurosci Res 2003;71:575–82.
[62] Lemire J. Vitamin D3: Autoimmunity and immunosuppression. In: Feldman D, edtior. Vitamin D, Amsterdam: Elsevier Academic Press 2005; 1753-1756.
[63] Penna G, Amuchastegui S, Giarratana N, et al. 1, 25-dihydroxyvitamin D3 selectively modulates tolerogenic properties in myeloid but not plasmacytoid dendritic cells. J Immunol 2007;178:145–53.
[64] Cohen MS, Mesler DE, Snipes RG, Gray TK. 1, 25-dihydroxyvitamin D3 activates secretion of hydrogen peroxide by human monocytes. J Immunol 1986;136:1049–53.
[65] Sardar S, Chakrabarty A, Chatterjee M. Comparative effectiveness of vitamin D_3 and vitamin E on peroxidation of lipids and enzymes of the hepatic antioxidant system in Sprague-Dawley rats. Int J Vit Nutr Res 1996;66:39–45.
[66] Wiseman H. Vitamin D is a membrane antioxidant Ability to inhibit iron-dependent lipid peroxidation in liposomes compared to cholesterol, ergosterol and tamoxifen and relevance to anticancer action. FEBS Lett 1993;326:285–8.
[67] Garcion E, Sindji L, Leblondel G, Brachet P, Darcy F. 1, 25-dihydroxyvitamin D3 regulates the synthesis of gamma-glutamyl transpeptidase and glutathione levels in rat primary astrocytes. J Neurochem 1999;73:859–66.
[68] Karasawa M, Hosoi J, Hashiba H, et al. Regulation of metallothionein gene expression by 1α, 25-dihydroxyvitamin D3 in cultured cells and in mice. Proc Natl Acad Sci USA 1987;84:8810–3.
[69] DeLuca HF, Cantorna MT. Vitamin D: Its role and uses in immunology. FASEB 2001;15:2579–85.
[70] Coleman DT, Fitzpatrick LA, Bilezikian JP. Biochemical mechanisms of parathyroid hormone activation. In: Bilezikian JP, edtior. The Parathyroids, New York: Raven Press 1994; 239-258.
[71] Heaney RP. The calcium economy. In: Weaver CM, Heaney RP, edtior. Calcium in Human Health, Totowa, New Jersey: Humana Press 2006; 145-162.
[72] Heaney RP. Calcium in systemic human health. In: Heaney RP, edtior. Calcium in Human Health. Weaver CM, Totowa, New Jersey: Humana Press 2006; 313-317.
[73] Heaney RP. Bone as the calcium nutrient reserve. In: Heaney RP, edtior. Calcium in Human Health, Weaver CM, Totowa, New Jersey, Humana Press Inc; 2006 p. 7-12.
[74] Awumey EM, Bukoski RD. Cellular functions and fluxes of calcium. In: Weaver CM, Heaney RP, edtiors. Calcium in Human Health, Totowa, New Jersey: Humana Press; 2006 13-37.
[75] Höck AD. Fatigue and 25-Hydroxyvitamin D levels. J Chronic Fatigue Syndr 1997;3:117–27.
[76] Höck AD. Divalent cations, hormones, psyche and soma: Four case reports. J Chronic Fatigue Syndr 2000;6(3/4):117–31.
[77] Stumpf WE, Privette TH. Light, vitamin D, and psychiatry. Role of 1, 25 dihydroxyvitamin D3 (soltriol) in etiology and therapy of seasonal affective disorder and other mental processes. Psychopharmacology 1989; 97:285–94.
[78] Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr 2003;89:552–72.

Please cite this article in press as: Hoeck AD, Pall ML. Will vitamin D supplementation ameliorate diseases characterized by chronic inflammation and fatigue? Med Hypotheses (2010), doi:10.1016/j.mehy.2010.09.032

[79] Ruscetti LombardiVC, FW Das, Gupta J, Pfost MA, Hagen KS, et al. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. Science 2009;326(5952):585–9.
[80] Zhang Y, Nakata K, Weiden M, Rom WN. Mycobacterium tuberculosis enhances human immunodeficiency virus-1 replication by transcriptional activation at the long terminal repeat. J Clin Invest 1995;95:2324–31.
[81] Müller F. Reactive oxygen intermediates and human immunodeficiency virus (HIV) infection. Free Radic Biol Med 1992;13(6):651–7.
[82] Griffin GE, Leung K, Folks TM, Nabel GJ. Induction of NF-kappa B during monocyte differentiation is associated with activation of HIV-gene expression. Res Virol 1991;142(2–3):233–8.

Please cite this article in press as: Hoeck AD, Pall ML. Will vitamin D supplementation ameliorate diseases characterized by chronic inflammation and fatigue? Med Hypotheses (2010), doi:10.1016/j.mehy.2010.09.032