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Vitamin D₃, nervous system and aging

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Summary This is a mini-review of vitamin D₃, its active metabolites and their functioning in the central nervous system (CNS), especially in relation to nervous system pathologies and aging. The vitamin D₃ endocrine system consists of 3 active calciferol hormones: calcidiol (25OH D₃), 1 α -calcitriol (1 α ,25(OH)2D₃) and 24-calcitriol (24,25(OH)2D₃). The impact of the calciferol hormone system on aging, health and disease is discussed. Low serum calcidiol concentrations are associated with an increased risk of several chronic diseases including osteoporosis, cancer, diabetes, autoimmune disorders, hypertension, atherosclerosis and muscle weakness all of which can be considered aging-related diseases. The relationship of many of these diseases and aging-related changes in physiology show a U-shaped response curve to serum calcidiol concentrations. Clinical data suggest that vitamin D₃ insufficiency is associated with an increased risk of several CNS diseases, including multiple sclerosis, Alzheimer's and Parkinson's disease, seasonal affective disorder and schizophrenia. In line with this, recent animal and human studies suggest that vitamin D insufficiency is associated with abnormal development and functioning of the CNS. Overall, imbalances in the calciferol system appear to cause abnormal function, including premature aging, of the CNS.

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1. Introduction

In the past decades, our knowledge about vitamin D₃ and its biological activity has significantly developed. Itself, vitamin D₃ is not biologically active suggesting that its classification as a vitamin is no longer valid. However, our hormonal system is fully dependent on an external supply of vitamin D₃ as a precursor to its active metabolites, the calciferol hormones. These hormones include calcidiol (25OH D₃, or

25-hydroxycholecalciferol, synthesized mainly in the liver and skin) (Lou et al., 2004; Peng et al., 2009), calcitriol (1 α ,25(OH)2D₃ (Demay et al., 1992) or 1 α ,25-dihydroxycholecalciferol), synthesized in the kidney and other tissues) and 24-calcitriol (24,25(OH)2D₃, or 24,25-dihydroxycholecalciferol), synthesized in several tissues (Bordier et al., 1978; Helm et al., 1996; Ornoy et al., 1978; van Driel et al., 2006). It has been proposed that all hydroxylated forms of calciferol can bind to the vitamin D receptor (VDR) and subsequently regulate gene expression (Harant et al., 2000). However, the typical serum concentrations of most of them are too low to produce any significant biological responses. All the calciferol hormones bind to VDR (NR111), which heterodimerizes with liver X receptors

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(LXR) and belongs to the subfamily 1 of nuclear receptors (NR1). Thyroid hormone receptors, THRA (NR1A1) and THRB (NR1A2) belong to the same subfamily and heterodimerize with LXR (Mooijaart et al., 2005). These hormonal system are, however, all dependent on exogenous supply of precursors. Calciferol hormone system is dependent on exogenous sun-induced or dietary vitamin D₃, just as thyroid hormone endocrinology is dependent on dietary iodine, or retinoic acid on dietary vitamin A. The second major change in our understanding is that calciferol hormones are not only important for bone development, but are also widely involved in health and the onset of various diseases, particularly as they relate to aging (Tuohimaa, 2008, 2009).

Calciferol hormone metabolism is strictly controlled by a reciprocal feedback system that exists between calcidiol and 1 α -calcitriol. Chronic administration of 1 α -calcitriol increases the metabolic clearance rate of calcidiol (Clements et al., 1992; Halloran et al., 1986) or decreases 1 α -calcitriol production with consequent depletion of stores (Reinholz and DeLuca, 1998). On the other hand, an administration of a high dose of calcidiol increases the metabolic clearance of 1 α -calcitriol (Reinholz and DeLuca, 1998). This suggests that the endocrinological feedback mechanisms are able to balance the sum effect of calciferol hormones.

The widely accepted paradigm postulates that circulating calcitriol is the active hormone (Trump et al., 2004), and that calcidiol needs to be activated within the cell through the action of 1 α -hydroxylase (CYP27B1) (Schwartz et al., 1998). However, this view is at odds with several important recent findings. First, calcidiol can easily enter the target cell through megalin-mediated endocytosis of the vitamin D binding protein (DBP)–calcidiol complex (Nykjaer et al., 1999). Calcitriol has 10 \times lower affinity to DBP, suggesting that calcitriol is hormonally less significant (Nykjaer et al., 1999; White and Cooke, 2000). Moreover, most of it is unbound in serum and there is a direct correlation between the megalin-mediated endocytosis and the action of calcidiol (Rowling et al., 2006). Second, the physiological concentration of calcitriol is \sim 1000-fold lower than that of calcidiol, but the VDR binding affinity of calcitriol (Scatchard) is 100-fold higher than that of calcidiol (Brown et al., 1999), whereas K_i as bonded energy shows only a 2-fold difference (Marshall, 2006). Thus, VDR is mainly occupied with calcidiol and if it were inactive it should act as a competitive inhibitor suppressing all the activity of calcitriol. Finally, when calcidiol is converted intracellularly to calcitriol it acts as an intracrine and autocrine regulator and should not be classified as a hormone (Atkins et al., 2007).

Why is serum calcidiol physiologically important? It seems that calcidiol better reflects clinical data than calcitriol, but calcidiol, according to present paradigm, is an inactive prohormone, whereas calcitriol is an active hormone. This discrepancy was enigmatic before our recent study (Lou et al., 2004) suggested that both are active hormones and act together. Here, we propose a model for calciferol hormone action in which the main circulating hormone is calcidiol and together with 24-calcitriol acts in concert with calcitriol on target cells. Our present hypothesis helps to understand why serum calcidiol is associated with chronic diseases and aging as well as the clinical benefits of vitamin D treatment. In the CNS, the blood–brain barrier does not allow macromolecules, such as calcidiol–DBP complex, to

enter. This suggests that megalin-mediated endocytosis plays an important role. Once calcidiol is available to neurons and glial cells, they are able to convert it via 1 α -hydroxylation to the more active 1 α -calcitriol. If this model is correct, we can classify calcidiol as a neuroactive hormone and 1 α -calcitriol as neurosteroid. The neurosteroid role of 24-calcitriol in CNS has so far not been demonstrated.

2. U-shaped risk of chronic diseases to serum calcidiol

There is accumulating evidence that both high and low serum calcidiol concentrations are associated with an increased risk of chronic diseases. Our study of 200,000 Nordic men suggested, for the first time, that prostate cancer risk and serum calcidiol levels are related in a U-shaped fashion (Tuohimaa et al., 2004). A similar finding was reported 3 years later (Faupel-Badger et al., 2007). A recent, vast report by the International Agency for Research of Cancer shows several U-shaped epidemiological risk curves to serum calcidiol concentrations such as risk of cardiovascular diseases and all cause deaths (IARC, 2008). Larger epidemiological studies on common chronic diseases are needed in order to verify how common the U-shaped risk curve is, including common diseases of the CNS. After those studies, it will be possible to determine what the optimal serum concentration of calcidiol is.

According to some studies, the present optimal serum calcidiol concentration is approximately 40–60 nmol/L (16–24 ng/ml) (Faupel-Badger et al., 2007; IARC, 2008; Tuohimaa et al., 2004). However, there is a need for larger, more comprehensive clinical and epidemiological studies (Mimouni and Shamir, 2009). Additionally, there is typically an increase in overall body fat with ageing, creating a larger distribution volume for the fat-soluble calcidiol, and the potential for characterizing patients as vitamin D deficient when, in fact, they are within optimal concentrations (Konradsen et al., 2008). Moreover, variations in circulating calcidiol concentrations is suggested to be a significantly heritable trait, based on a recent analysis of 1762 elderly men and women in community-based health care (Shea et al., 2009). It is evident that there has been adaptation to UV-B irradiation such as the skin color, therefore there might be population differences in the optimal calcidiol serum concentration. This implies that further studies of optimal calcidiol serum concentrations for disease prevention are necessary among different populations and groups of a population.

3. Calciferol hormones and diseases of the central nervous system

Accumulating evidence suggests that calciferol hormones are involved in brain function (Garcion et al., 2002). Genes encoding vitamin D₃-25-OHase and 1 α -hydroxylase (CYP27B1), the enzymes which metabolize vitamin D₃ into calciferol hormones, are expressed in neurons and glial cells (Neveu et al., 1994b; Zehnder et al., 2001). Moreover, the VDR has been localized in neurons and glial cells (Prufer et al., 1999).

Calciferol hormones are known as neuroactive compounds regulating behavioral functions such as anxiety (Kalueff et al., 2006b). Hypovitaminosis is associated with an increased risk of multiple sclerosis (Schwartz, 1992),

seasonal affective disorder (SAD) (Gloth et al., 1999), schizophrenia (Mackay-Sim et al., 2004; McGrath et al., 2004), Parkinson's disease and Alzheimer's disease (Evatt et al., 2008; Oudshoorn et al., 2008). It has been proposed that vitamin D deficiency could also be associated with autism (Barnevik-Olsson et al., 2008; Cannell, 2008), although there is only indirect evidence for this hypothesis. Furthermore, mood and cognitive performance appear to be vitamin D-dependent to some extent (Wilkins et al., 2006).

Also a few double-blind placebo-controlled prevention trials support the hypothesis that calciferol hormones are significantly involved in several chronic diseases including those of CNS and they could be effectively used in preventive medicine (Zittermann, 2003). However, it is evident that more studies are needed before final conclusions can be made, especially in the case of CNS pathologies.

In addition to the diseases of CNS, calciferol hormone insufficiency can increase the risk of other aging-related diseases such as osteoporosis (Cranney et al., 2008; Holick and Chen, 2008; Ruohola et al., 2006), cancers (Giovannucci et al., 2006), muscle weakness (Montero-Odasso and Duque, 2005; Rimaniol et al., 1994), respiratory infections (Laaksi et al., 2007), autoimmune diseases (Ponsonby et al., 2005; Van Etten et al., 2003), diabetes (Hypponen et al., 2001), hypertension (Forman et al., 2008; Margolis et al., 2008; Scragg et al., 1992), cardiovascular diseases (Scragg et al., 1990; Zittermann and Koerfer, 2008) and congestive heart failure (Zittermann et al., 2006). Hypovitaminosis D₃ is independently associated with all-cause mortality (Melamed et al., 2008), see a summary of these data in Table 1.

4. Calciferol hormones and aging of the central nervous system

Aging has significant effects on calciferol endocrine system. The cutaneous production of calciferol hormones decreases in elderly people (MacLaughlin and Holick, 1985) and the metabolic clearance rate is increased because of a high expression of 24-hydroxylase. Furthermore, elderly people are less exposed to sunlight. On the other hand, the altered calciferol hormone balance seems to enhance aging (see below).

Aging of the CNS is a central event in the aging of a whole organism. For example, mutations that downregulate insulin-like growth factor (IGF) and growth hormone signaling limit body size and prolong lifespan in mice (Brown-Borg, 2008). Sirtuins are known to play important role in aging, also modulating in IGF-signaling (Wenzel, 2006). In all vertebrates, these somatotrophic hormones are controlled by the neuroendocrine brain system. Hormone-like regulations discovered in nematodes and flies suggest that IGF activity in the nervous system can determine lifespan, but it is unknown whether this applies to higher order organisms (Kappeler et al., 2008). However, the precise role of calciferol hormones in the aging of CNS remains to be extrapolated, and the same applies to biomarkers of aging in the brain, which we are only beginning to understand (Crimmins et al., 2008).

The human brain is capable of locally synthesizing the active calciferol hormones and widely expresses the VDR in the cortex, cerebellum, mesopontine area, diencephalon, spinal cord, amygdala, hypothalamus and hippocampus

Table 1 Chronic diseases associated with a low calcidiol serum concentration (vitamin D₃ insufficiency) and the strength of the evidence.

Disease	Evidence	Reference
Osteoporosis	+++	Cranney et al. (2008)
Osteomalasia	+++	Cranney et al. (2008)
Rickets	+++	Holick and Chen (2008)
Stress fractures	+	Ruohola et al. (2006)
Myopathy	++	Montero-Odasso and Duque (2005)
Solid cancers	++	Tuohimaa (2008)
Psoriasis	++	Fogh and Kragballe (2004)
Atopic dermatitis	+	Schauber and Gallo (2008b)
Rosacea	+	Schauber and Gallo (2008a)
Loss of hearing	+++	Brookes and Morrison (1981) and Zou et al. (2008)
Loss of balance	+	Minasyan et al. (2009)
Rheumatoid arthritis	++	Ranganathan (2009)
Inflammatory bowel	++	Zittermann (2003)
Atherosclerosis	++	Zittermann (2006)
Congestive heart failure	+	Zittermann et al. (2006)
Hypertension	++	Margolis et al. (2008)
Diabetes I and II type	+	Forouhi et al. (2008) and Hypponen et al. (2001)
Multiple sclerosis	++	Cantorna (2008)
Allergic encephalomyelitis	+	Garcion et al. (1997)
Seasonal affective disorder	+	Gloth et al. (1999)
Alzheimer's disease	+	Evatt et al. (2008)
Parkinson's disease	+	Evatt et al. (2008)
Schizophrenia	+	McGrath et al. (2004)
Autism	+	Cannell (2008)
Epilepsy	++	Kalueff et al. (2006c)

(Eyles et al., 2005). In *C. elegans* DAF-12 is a gene encoding a nuclear receptor (NR) known to have a role in organism longevity and disease at old age. Analysis of human NRs, based on sequence similarity, suggests that VDR is a close homologue of DAF-12 (Mooijaart et al., 2005). The ligand of DAF-12, 7-dehydrocholesterol, is a precursor of vitamin D₃ and is hydroxylated by DAF-9, a homolog of CYP27B1, 1 α -hydroxylase (Rottiers et al., 2006). DAF-12 and VDR as well as thyroid and retinoic acid receptors belong to the subfamily 1 of NRs, which typically heterodimerize with RXR, are involved in homeostasis of steroid hormones (Wang and Tuohimaa, 2007) and detoxification of xenobiotic compounds (Kutuzova and DeLuca, 2007). There is a trade-off between reproduction and longevity (Westendorp and Kirkwood, 1998). Human longevity necessitates more than average investments in somatic maintenance, because an excess of radical oxygen species (ROS) damage macromolecules and lead to early death. Therefore, subfamily NR1 receptors, especially VDR, are candidates for longevity regulation by controlling excess of free radicals and by metabolizing toxic environmental compounds.

By examining gene expression changes in aging neurons, it is generally hypothesized that the mechanisms underlying CNS aging involve genomic instability, neuroendocrine dysfunction, production of oxidative compounds, altered calcium metabolism and inflammatory neuron damage (Lee et al., 2000). Calciferol hormones and the VDR have been implicated to have a regulatory effect in most, if not all, of these aging mechanisms.

Microarray studies have found that calcitriol induces the expression of GADD45 α , a protein involved with DNA repair and global genome stability, illustrating the genoprotective actions vitamin D and VDR (Akutsu et al., 2001; Galbiati et al., 2003). Neuroprotective actions of calciferol hormones are also believed to be modulated by an upregulation of neurotrophic factor nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) (Neveu et al., 1994a; Wang et al., 2000). After experimentally induced ischemia, calcitriol was observed to increase the activity of glial heme oxygenase-1 an enzyme responsible for converting free heme into powerful endogenous antioxidants, biliverdin and bilirubin (Oermann et al., 2004). Calcitriol has also been found to inhibit the synthesis of inducible nitric oxide synthase (iNOS), an enzyme responsible for generating nitric oxide, known to cause damage to neurons and oligodendrocytes at high concentrations (Garcion et al., 1998). Vitamin D metabolites are also involved in a number of neuronal-glial cell signaling pathways which further support the role of calciferol hormones in waste management and neuroprotective actions (Brachet et al., 1997; Garcion et al., 2002). It is generally accepted that the primary biological function of vitamin D is Ca⁺⁺ metabolism, since vitamin D and the VDR, acting in parallel with other hormones, regulate Ca⁺⁺ transport in renal and intestinal tissues in addition to bone mineralization (Haussler et al., 1998; Li et al., 2002, 2004).

Interestingly, chronic calcitriol treatment is able to reduce Ca⁺⁺-mediated hippocampal biomarkers of aging by downregulating the L-type voltage-sensitive Ca⁺⁺ channel (Brewer et al., 2006). Moreover, calcitriol is also able to induce the synthesis of Ca⁺⁺ binding proteins, further reducing potentially toxic extracellular concentrations of Ca⁺⁺ (de Viragh et al., 1989). Vitamin D deficiency has been

suggested as a primary etiology of autoimmune diseases such as Crohn's, rheumatoid arthritis and inflammatory bowel disease (Zittermann, 2003) and autoimmune diseases of CNS (Cantorna, 2008; Kalueff et al., 2006d). In these autoimmune diseases, Helper T cells misdirect the immune response against self proteins causing an exaggerated release of inflammatory cytokines (IFN- γ , IL-1, IL-2, IL-5). Calcitriol directly targets Helper T cells modulating, most often down-regulating, the release of these inflammatory cytokines leading to a suppression of autoimmune responses (Bouillon et al., 2008b; Cantorna et al., 2004; Tsoukas et al., 1984).

Important support to the vitamin D-CNS-aging hypothesis also comes from recent mouse models. We have used two strains (129S1 and NMRI) of vitamin D receptor knockout mice (VDR-KO) and 1 α -hydroxylase KO mice for behavioral, biochemical and morphological studies. These mice survive only when they are fed with a special calcium-rich diet. After 6 months of age, they show clear symptoms of premature aging such as wrinkling of the skin, hair and weight loss, muscle atrophy (Keisala et al., 2009), immunological deficiency (Bouillon et al., 2008a) osteoporosis and ectopic calcification in the thalamic area of the brain (Kalueff et al., 2006a). Behavioral studies of VDR-KO mice report increased anxiety, abnormal grooming, pup cannibalism, impaired nest-building and neophobia (Kalueff et al., 2004, 2005a,b; Keisala et al., 2007; Minasyan et al., 2007). Furthermore, the VDR-KO mice develop hearing and balance defects earlier than wild-type littermates (Minasyan et al., 2009; Zou et al., 2008). The balance defect is not due to morphological abnormalities in the CNS, since cerebellar flocculus shows a normal development (Keisala et al., 2009). There are no functional defects in olfaction or in gustation. Moreover, it is interesting that balance defects, skin aging and hair loss are not observed in 1 α -hydroxylase KO mice, suggesting that these characteristics require a functional VDR or that calcitriol might be substituted with calcidiol and 24-calcitriol.

5. Both hypervitaminosis D₃ and hypovitaminosis D₃ cause premature aging

Fibroblast growth factor 23 (FGF-23) (DeLuca et al., 2008; Razzaque et al., 2006) has recently emerged as a key mediator/hormone of early aging and its effects appear to be mediated by an excess of calcitriol. The early aging phenotype includes thin skin, intestinal atrophy, spleen atrophy, muscle atrophy, weight loss, short life prognosis, osteoporosis and atherosclerosis. Due to tight physiological regulation of hormonal forms of vitamin D₃ by 24-hydroxylase, which is modulated by physiological concentrations of calcidiol, hypervitaminosis D₃ is rare in humans (Lou et al., 2004). However, during the early period of synthetic vitamin D₃ substitution/fortification some intoxications occurred. After the Second World War in Europe, especially in Germany, children received extremely high oral doses of vitamin D₃ and suffered hypercalcemia, nephrocalcinosis, early aging, cardiovascular complications and early death, supporting the possibility that hypervitaminosis D₃ can accelerate aging (Bransby et al., 1964; Markestad et al., 1987; Oliveri et al., 1996; Ronnefarth and Misselwitz, 2000). Unfortunately, no attention to a possible premature aging of CNS has been paid in those studies.

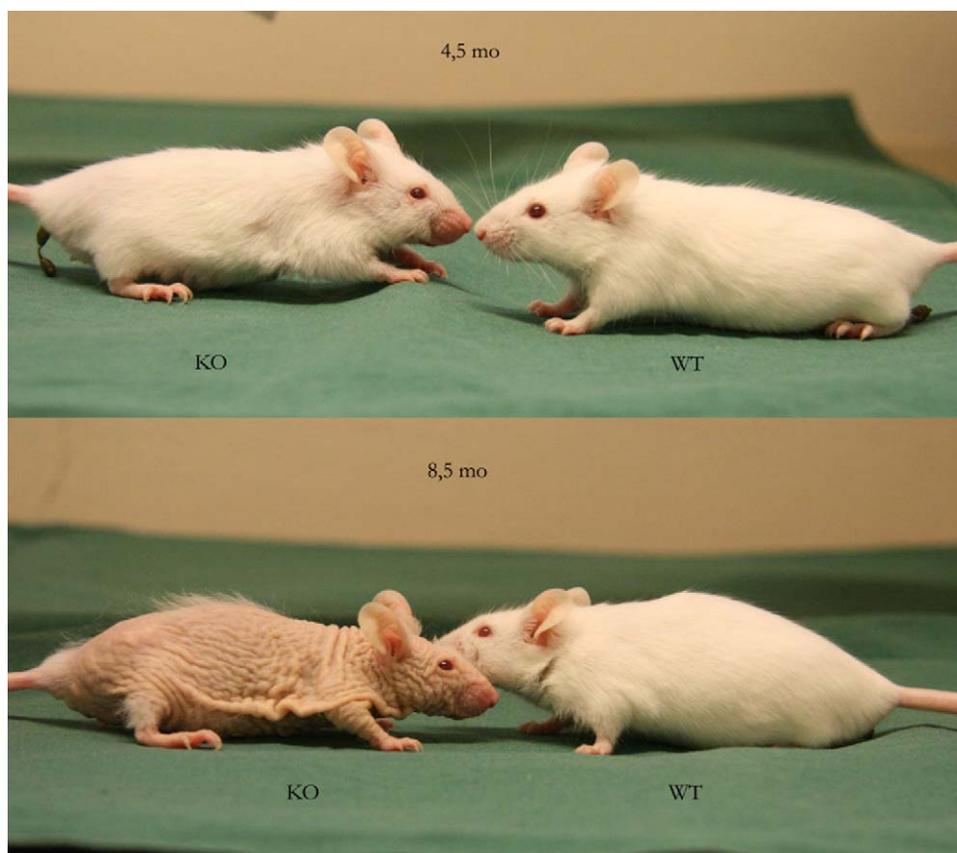


Figure 1 Premature aging of skin of vitamin D receptor (VDR) knockout mice (KO) is visible at the age of 8–9 months. The amount of subcutaneous fat is low and the skin wrinkling is clear compared to the wild type (WT) mice. Alopecia in VDR KO mice begins rostrally at the age of 4 months, and becomes particularly obvious at the age of 8–9 months.

Interestingly, the aging phenotypes of hypovitaminosis mice (VDR and 1α -hydroxylase mutants) (Fig. 1) are quite similar to those of hypervitaminosis D₃ (Tuohimaa, 2009). As described above, insufficiency of calciferol hormones may accelerate the development of diseases of CNS. A recent study suggested that hypovitaminosis D₃ may cause a premature aging of cognitive functions (Buell et al., 2009).

Thus, both a lack and an excess of calciferol hormones enhance aging. Aging seems to show a U-shaped response curve to calciferol hormone concentrations (Fig. 2), and, therefore normovitaminosis D₃ seems to be important for delaying aging.

6. Conclusion

While it is currently unknown how premature aging and the associated chronic diseases correlate with calcidiol concentrations, it appears that premature aging, cancer and chronic diseases share the same mechanisms (Irminger-Finger, 2007). Initial events affect the genome, causing telomere shortening or accumulation of DNA damages, which are modulated by the tumor suppressor protein, p53. Additional mediators of aging and cancer are telomerase reverse transcriptase, FGF-23, insulin-like growth factor signaling system and NF- κ B, all of which are regulated by calciferol hormones (Keisala et al., 2009; Tuohimaa, 2009). Hormonal forms of vitamin D₃ appear to control basic mechanisms of aging and related diseases, and determining the optimal serum concentration of calcidiol is an important question for preventive medicine. A new model of aging is presented here (Fig. 2), in which both too high and too low activity of calciferol hormone activity seems to enhance aging, whereas optimal concentrations appear to delay aging.

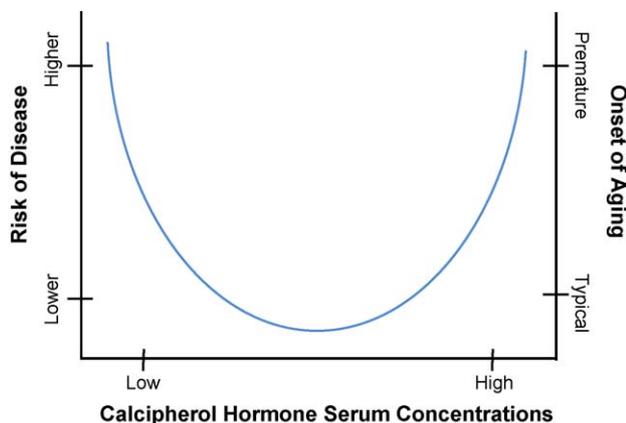


Figure 2 Vitamin D-aging hypothesis. Both low and high action of calciferol hormones causes premature aging and thus aging-related diseases (including diseases of CNS) appear earlier. Therefore there might be an optimal serum concentration, which is able to delay aging.

Conflict of interest statement

None declared.

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