Treatment of vitamin D deficiency in Dutch nursing home residents

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door
Victor Gerardus Marinus Chel
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promotor : prof.dr. P.T.A.M. Lips

copromotoren : dr. M.E. Ooms
dr. S. Pavel

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Chapter 1

General introduction

1.1. History of vitamin D

The origin of vitamin D probably dates back more than 750 million years, when it was produced by ocean dwelling phyto- and zooplankton while exposed to sunlight [1-3]. Now in most animals, plants and fungi exposed to sunlight, vitamin D is photosynthesised [1-3]. The precise biologic function of vitamin D in invertebrates is unknown, in plants it possibly promotes root growth and in vertebrates it increases the absorption and regulates the extracellular levels of calcium and phosphate for the skeletal mineralisation, growth and many other biological processes [1-3]. Vitamin D can be found in the livers of all existing vertebrate classes, with no known exceptions, and phylogenetically the levels of vitamin D in vertebrates positively correlate with the presence of bone.

Severe vitamin D deficiency causes rickets in children. The cartilage does not mineralise, and the epiphyseal zone hypertrophies leading to swollen joints. In adults it causes osteomalacia which is characterised by the accumulation of nonmineralised bone matrix [3]. Classic bony deformities as noted in rickets were already described in ancient Roman medical writings from the 1st and 2nd centuries by Soranus and Galen [4]. The first description of rickets is credited to Daniel Whistler, an English medical student in Leyden. In 1645 he wrote a monograph titled "Inaugural medical disputation on the disease of English children which is popularly termed the rickets" [4]. The incidence of rickets or English disease continued to increase and at the turn of the 20th century this bone disease was rampant among the underprivileged children in industrialised cities in Europe and the United States [1, 4].

In 1822 Jędrzej Śniadecki probably was the first one to describe the role of sunlight in preventing and curing rickets in children living in Warsaw [1]. In 1890 Palm studied the relationship between the incidence of rickets and its geographical distribution. He concluded that rickets was caused by lack of sunlight exposure [4]. In Germany, 30 years later, in 1919, Kurt Huldschinsky succeeded in demonstrating the healing qualities of ultraviolet (UV) radiation therapy in rickets by using a mercury vapor quartz lamp as artificial sunlight [1].

A dietary factor as a cause for rickets was proposed one year earlier in London, in 1918, by Edward Mellanby. He demonstrated, in experiments with dogs, that rickets could be cured with cod liver oil, which in folklore practice was already widely appreciated for its supposed medical benefits [1, 4]. In Vienna, Harriette Chick confirmed the preventive and therapeutic effect of cod liver oil and sunlight on rickets by controlled clinical studies between 1919 and 1922 [4]. The recognition of cod liver oil as a specific remedy against rickets was found in German medical literature as early as 1824 [4].

In France, in 1827, Pierre Bretonneau described curing a 15 month child from rickets with cod liver oil [1]. His pupil, Armand Trousseau, later wrote "*I am also strongly led to believe, that rickets and osteomalacia are the same disease, by the fact, that both are wonderfully combated by the same medication. This medication may be considered as really heroic in the treatment of rickets: it consists in giving cod liver oil, and, in a more general way, fish oil ...*" [5]. Initially it was assumed that the vitamin A in cod-liver oil was responsible for the healing effect on rickets. In 1922 however, vitamin D was identified

In the United States by Elmer McCollum who isolated an "*anti-rachitic substance*" from oxidised (oxidation destroys vitamin A) cod liver oil which "*specific property was to regulate the metabolism of the bones*". This substance was the fourth in the sequence of discovery of vitamins; hence it was called vitamin D [4]. In 1924 Steenbock and Black, as well as Hess and Weinstock, found, by exposing a variety of food to UV radiation, that irradiated food developed anti-rachitic properties [1]. Around this period an almost complete eradication of rickets in the western world was accomplished because of the emerging therapeutic use of adequate UV and sunlight exposure and cod liver oil (vitamin D) [2].
Some 40 years later, Anderson et al in 1966 and Chalmers et al in 1967, drew attention to osteomalacia being common in older people [2, 6] In 1969 Chalmers reported that osteomalacia often was associated with hip fracture [2].
Osteomalacia and rickets are caused by a severe vitamin D deficiency. A less severe vitamin D deficiency, often described as vitamin D insufficiency, causes stimulation of the parathyroid glands, which may lead to high bone turnover, cortical bone loss and fractures [2]. Over the last 30 years many papers have been published on the multiple health problems in older people associated with vitamin D deficiency and insufficiency.

1.2. Production and metabolism of vitamin D

Vitamin D exist in two major forms: vitamin D2 (ergocalciferol) of vegetable origin and vitamin D3 (cholecalciferol) of animal origin. When ergosterol (a steroid found in some plants but largely in fungi) is irradiated with ultraviolet B (UV-B) light (280-315nm), previtamin D2 is formed. When 7-dehydrocholesterol, a cholesterol precursor, is irradiated with UV-B in the animal and human skin, previtamin D3 is formed, which is immediately converted to vitamin D3 in a heat-dependent process. There is no danger of vitamin D intoxication by this pathway because UV-B breaks down excessive amounts of (pre) vitamin D into inactive photoproducts [3, 7, 8]. Vitamin D made in the skin or ingested in the diet is transported by the bloodstream bound to a vitamin D binding protein (DBP) [7]. Vitamin D (hereafter "D" represents D2 or D3) itself is inert. In the liver it is converted to calcidiol or 25-hydroxy-vitamin D (25(OH)D) by 25-hydroxylase (CYP2R1) [9]. Although calcidiol is biologically inert, it is the major circulating form of vitamin D which is used by clinicians to determine vitamin D status [7]. Mainly in the distal tubules of the kidney calcidiol is converted to the biologically active form calcitriol or 1,25-dihydroxy-vitamin D (1,25(OH)2D), by 1α-hydroxylase (CYP27B1) [7, 9]. This last step is under tight metabolic control by a parathyroid hormone (PTH) feed-back mechanism: PTH stimulates the production of calcitriol and calcitriol inhibits PTH release (*figure 1*). Also serum phosphate, calcium, and other factors can either increase or decrease the renal production of calcitriol [2, 3, 7]. In recent years it has become apparent that 1α-hydroxylase is present in many organs, such as bone, brain, intestine, lung and lymphatic tissue, but it is not known whether this contributes to the serum level of 1,25-dihydroxyvitamin D. In addition, the extrarenal hydroxylation is not under the above mentioned feedback control, but it may depend on the amount of available substrate, i.e. 25-hydroxyvitamin D.

Vitamin D is stored in adipose tissue, skeletal muscle and the liver. Adequate stores can provide vitamin D for many months. In humans the biological half-life of circulating 25(OH) D is approximately 3-4 weeks, while that of 1,25(OH)2D is only approximately 6-8 hours [3, 10-13]. The liver is the major site of vitamin D catabolism and a range of cytochrome P450 enzymes are involved (e.g. CYP27A1, CYP24A1) [3, 9]. In the liver vitamin D ultimately is catabolised to highly polar, biological inert, water-soluble metabolites which are excreted in the bile. Only about 2% is excreted through the urine [3, 7, 14].

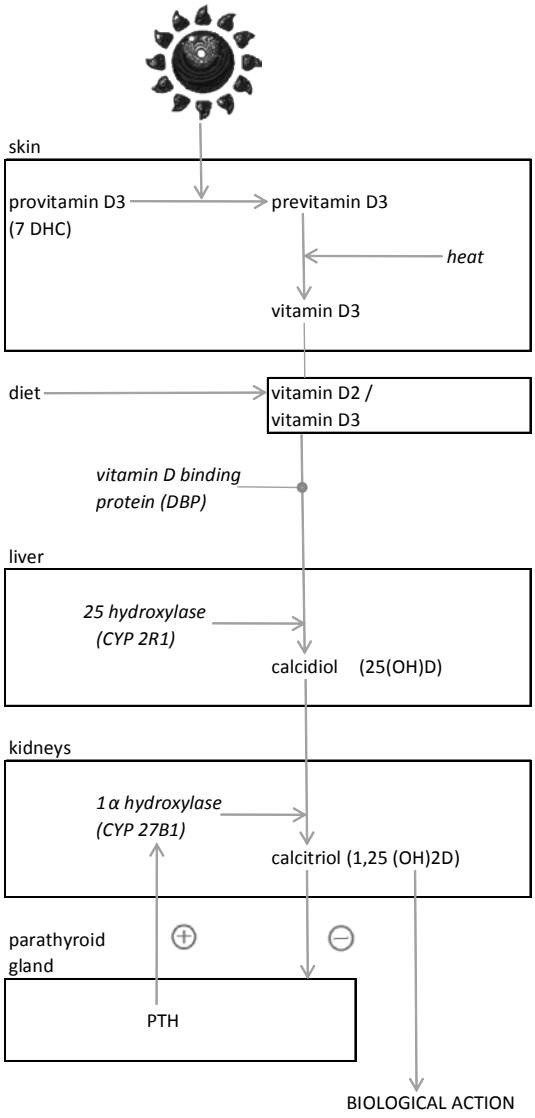

figure 1

1.3 Actions of vitamin D

Vitamin D should be regarded as a prohormone. It is produced in the skin, the production of the active metabolite is under strict control and it is transported by the bloodstream to target tissues where it acts through a receptor mediated, genomic mechanism [3, 15]. After binding to a specific vitamin D receptor (VDR), it stimulates gene transcription and cell differentiation [3]. There are indications that 1,25-dihydroxy vitamin D has more rapid, non-genomic effects as well, acting at the level of the cell membrane (of e.g. muscle tissue) [3, 15].

The vitamin D receptor belongs to the steroid hormone receptors [3, 9, 16, 17]. It is thought to be present in up to 38 tissues [16]. VDR is clearly present in cells of the intestinal epithelium, renal tubules, parathyroid glands, skin, mammary epithelium, pancreas (β-islet cells), pituitary gland, skeleton (osteoblasts and chondrocytes), immune system (monocytes, macrophages and T-lymphocytes) and germ tissues [17]. About the presence of the VDR in human muscle cells conflicting results are reported [17, 18]. The intestines, kidney, parathyroid glands and bone are the tissues with the highest VDR content, all of which are involved in calcium homeostasis and bone metabolism [17].

Vitamin D was first recognised for its role in bone health with vitamin D deficiency causing rickets, osteomalacia and osteoporosis via impairment of intestinal calcium absorption. After the binding of calcitriol to a VDR in the intestine, the synthesis of several proteins, which participate in the calcium-transport from the intestinal lumen into the bloodstream, is stimulated [2]. The action of calcitriol on bone is not well understood; it appears to have a dual function [2,3]. The anabolic effect on bone mineralisation appears to be indirect by stimulating the calcium and phosphate supply, mainly by absorption from the gut [2]. Calcitriol stimulates the osteoblasts to produce osteocalcin and alkaline phosphatase and decreases the production of type I collagen in fetal rat calvaria [2, 19]. On the other hand, calcitriol stimulates bone resorption in vitro. This may be the result of increased production of osteoclasts from monocytic stem cells in the bone marrow, or due to an effect on osteoclasts already present on the bone surface, either directly or mediated through osteoblasts [2, 3, 20]. The bone remodeling sequence, by which new osteons are formed, starts with the resorption of existing bone, by osteoclasts. This may be triggered by microtrauma, e.g. fissures or microfractures. Then the new unmineralised bone matrix (osteoid) is constructed by osteoblasts. Subsequently the osteoid is mineralised in two phases: a fast primary mineralisation which occurs within a few days, accumulating about half of the bone mineral, increasing the density to 1.4g/cm3 and a slower secondary mineralisation which increases the density to 1.9g/cm3 within 6 months [2, 21]. Older, completely mineralised high-density bone is associated with low bone turnover [2].
Low serum 25-hydroxyvitamin D levels lead to secondary hyperparathyroidism via lowered serum calcium levels. Secondary hyperparathyroidism leads to an increase in bone turnover, which is associated with primarily cortical bone loss (the trabecular bone is relatively preserved), osteoporosis and fractures [2].

Vitamin D supplementation combined with adequate calcium intake decreases the BMD-loss in postmenopausal women and older men and it convincingly lowers the fracture risk of persons aged 65-70 years and older, especially in women. It is however still questioned whether vitamin D supplementation alone, without adequate calcium intake, also lowers the fracture risk [22].
Vitamin D deficiency is also associated with muscle weakness, muscle pain, sarcopenia, fatigue, impaired balance, increased body sway, decreased physical performance, neurological dysfunction and risk of falling [23-29]. Multiple mechanisms by which vitamin D could affect muscle function have been suggested. Apart from a possible direct genomic effect and a more rapid, non-genomic effect at the level of the muscle cell membrane, also indirect effects are thinkable [15, 29]. It is for example possible that muscle weakness occurs due to metabolic derangements resulting from vitamin D deficiency; notably hypophosphatemia. Vitamin D can stimulate phosphate absorption and it has been shown that phosphate supplementation corrects muscle weakness in vitamin D deficient rats [29, 30].
Vitamin D supplementation improves myopathy and increases type II muscle fibres which are fast-twitch; the first to be recruited when trying to prevent a fall [2, 31, 32].
Studies on vitamin D supplementation and muscle strength however show conflicting results [22, 29, 32, 33].
Vitamin D is also associated with non-muscular effects which could influence fall risk:

- neurologic dysfunction: VDRs and the enzyme 1-α-hydroxylase are found to be present in the cerebral cortex and cerebellum which may influence neurotransmitter activity or neurotropic factor production. Vitamin D could also influence emotional function and cognitive function (over 40% of hip fracture patients have cognitive impairments). Depression and cognitive dysfunction are associated with vitamin D deficiency in epidemiological studies [29, 34-36]. Vitamin D was also found to be associated with reaction time and balance (but not with muscle strength) in older fallers [37].
- vestibular function: VDR deficiency in mice was found to be associated with vestibular dysfunction and decreased balance function [38].
- alterations of sex steroid levels: Testosterone has a positive effect on bone and muscle [29] and the VDR is present in the testis [17]. Seasonal fluctuation of serum calcidiol is corresponding with a distinct seasonality of circulating testosterone [39] and vitamin D supplementation was found to increase total testosterone in a study with 54 vitamin D deficient men [40].

It is altogether considered plausible that vitamin D supplementation, especially when combined with adequate calcium intake, lowers the risk of falling in older people, aged 70 years and older with low calcidiol serum levels or those not living independently [22, 29, 41-43].

In recent years an increasing number of studies have suggested that vitamin D deficiency and insufficiency contribute to the development of all sorts of chronic diseases. The number of adequately controlled clinical trials in support of a causative association

between vitamin D deficiency and insufficiency and disease incidence is however small compared to the many observational studies. Furthermore the assays used for measuring 25(OH)D often lack sufficient standardisation and in many studies little attention was paid to baseline status. Only weak associations between low calcidiol serum levels and disease were found, and the mechanisms by which vitamin D could play a role in the pathogenesis are often not known [2, 44-46].
The association between high serum levels of vitamin D and a lower risk of the following conditions are however considered to be plausible: autoimmune disease; infections; colorectal cancer; cardiovascular disease and diabetes type II. It is not clear yet whether vitamin D supplementation will have a beneficial effect on these conditions [22, 36, 47-65].
In regards to the association with infections, it is interesting to realise that we only recently begun to understand why the treatment of patients with tuberculosis in sanatoria could have been effective. Vitamin D can enhance macrophage phagocytosis of Mycobacterium Tuberculosis and increase the production of the antimicrobial peptide cathelicidin, killing intracellular M. Tuberculosis [66, 67]. In the mountain resorts the patients had obligatory rest, they consumed nourishing food and were regularly exposed to sunlight. The increased production of vitamin D might have provided them with increased protection against Mycobacteria.
Finally, apart from the known associations with conditions which often have a profound effect on the quality of life of institutionalised older people, low serum calcidiol is also associated with increased mortality in this group and it is considered plausible that in institutionalised older people (predominantly elderly women) vitamin D in the form of vitamin D3 (cholecalciferol) decreases mortality [68, 69].

1.4 Vitamin D status in older people

The serum concentration of 25(OH)D is the best determinant of vitamin D status [2, 7, 70]. Vitamin D deficiency can be defined according to health-based reference limits (i.e based on avoidance of adverse health outcomes for the skeleton) using biological indices (e.g hypocalcemia, elevated PTH, alkaline phosphatase levels) or to population-based reference limits [2]. It may be more appropriate to use health- based limits since reference groups often differ and serum calcidiol depends on life style and environmental characteristics [2]. Health-based reference values for serum calcidiol are higher than population-based values [2]. A functional health-based classification can be made by using serum PTH, bone turnover markers, or even bone mineral density [71]. Although it is difficult to formulate exact limits (i.e. the vitamin D levels leading to a rise in PTH in a Dutch study (30 nmol/L = 12 ng/ml) are different from those in a French study (78 nmol/L = 31 ng/ml) [2, 3, 72]) most investigators agree that serum 25(OH)D should be higher than 50 nmol/L (20ng/ml) [2, 22, 7]. This is the required level according to the Institute of Medicine (2011). The Dutch Health Council set the required level for adults at 30 nmol/l and for older persons at 50 nmol/l (Gezondheidsraad 2008, 2012). Several experts and the Endocrine Society Guideline expressed the opinion that the required level should be 75 nmol/l (30 ng/ml) [7, 23, 72-75].

The following staging is often used [2,16]: mild vitamin D deficiency or vitamin D insufficiency: serum 25 (OH)D = 25-50 nmol/L = 10-20 ng/ml; moderate deficiency: serum 25(OH)D = 12.5-25 nmol/L = 5-10 ng/ml and severe deficiency: serum 25 (OH)D = < 12.5 nmol/L = < 5 ng/ml.

Serum calcidiol levels are lower in European countries than in the United States. Traditional risk groups for vitamin D deficiency and insufficiency include pregnant women, children, non-western immigrants and older people [2, 70, 76]. In residents of homes for the elderly, nursing home residents and in patients with hip fracture vitamin D deficiency is very common [2, 3].

1.5 Prevention and treatment of vitamin D deficiency in older people

Vitamin D deficiency can be prevented or treated by exposure to sunlight, artificial UV irradiation, dietary vitamin D intake and by oral or parenteral supplementation.
How much vitamin D is produced in the skin by the UV-B in sunlight depends on the time of day, season of the year, latitude, aging, sunscreen use and degree of skin pigmentation [77]. At a latitude of 51°N (Edmonton Canada), which is comparable with the Netherlands, (latitude: 52°N), photosynthesis of previtamin D3 only occurs from April till October [78]. It has been shown that regular short (13 min) midday exposures to summer sunlight on a cloudless day while informally dressed (35% bare skin) three times weekly over a 6 week summer period will lead to vitamin D sufficiency: 25(OH)D ≥ 50 nmol/L = 20 ng/ml [79]. Individuals with dark skin often require an exposure which is 5 to 10 times longer than those with fair skin in order to produce the same amount of vitamin D [75]. The use of a sunscreen with an SPF of 30 reduces the photosynthesis of previtamin D3 by approximately 95% [79].
The aged skin has a decreased capacity to produce vitamin D: at 70 years of age the capacity has decreased by approximately 75% compared with a 20 year old person [79]. Exposure to sunlight while sitting inside behind glass windows is not effective since glass will absorb all UV-B irradiation [79].

Only few foods naturally contain vitamin D (i.e fatty fish, egg) therefore it is difficult to obtain adequate vitamin D levels by dietary vitamin D alone [22, 79]. The dietary vitamin D intake of older people in the Netherlands is approximately 100 IU/day (2.5 mcg) [80].
In the Netherlands margarine, low-fat spreads and frying products are fortified with vitamin D, containing 3 IU (0.075 mcg) cholecalciferol/g. Since 2007 it is permitted to fortify foods in the Netherlands with a maximum of 4.5 mcg /100 kcal [22, 80].

Based on the skeletal benefits and the requirements for fracture prevention [81], The Health Council of the Netherlands has recently set the target serum 25(OH)D level at 50 nmol/L (20 ng/ml) for older persons with a corresponding advice to the entire group of persons aged >70 years to take a daily supplement of 20 mcg (800 IU) vitamin D3,

cholecalciferol (The target value for the serum 25(OH)D level is the value above which (almost) everyone in the Netherlands has a sufficient supply) [22]. With a daily dose of 20 mcg (800IU) the mean serum level of 25(OH)D will increase to approximately 70 nmol/L within 3 months [82]. This recommended dose is safe and side effects are almost nonexistent. The maximum tolerable daily dose is 4000 IU [83].

1.6. Nursing homes in the Netherlands

Most Western countries have some kind of long-term care facilities for older people. In the Netherlands most of the people aged over 65 years (94%) live independently in their own houses. Approximately 165,000 (6%) live in residential homes or nursing homes (some 100,000 in residential homes and 65,000 in nursing homes [84]. Between 2000 and 2008 the average age of residential home and nursing home residents increased from 84 to 85. The percentage of women living in these institutions remained constant during this period: 77% [84]. In 2008 64,951 nursing home residents aged 65 and older were counted [84]. In the same year, according to "Statistics Netherlands" (CBS), 30,764 people aged 60 years and older died in a nursing home: the number of deaths in Dutch nursing homes in 2008 is approximately 47/100 person years (nursing home residents aged 65 and older (somatic and psychogeriatric)) [85].
The mean time of admission in nursing homes is generally estimated at 1.5-2 years.
In 2009 The Netherlands counted 479 nursing homes, 1,131 residential homes and 290 residential homes with nursing home-wards [86]. Nursing homes house disabled persons with chronic somatic or psychogeriatric conditions, mainly frail older people who are not able to perform most activities of daily living (ADL) themselves and who need plural, more complex, continuing care, treatment and monitoring, which are beyond the range of home care services or the service in residential homes [87]. In the Netherlands, the "elderly care physician" (former "nursing home physician") is an officially recognized medical specialisation and Dutch nursing homes employ not only nursing staff, but also their own medical, paramedical and psychosocial staff, including the elderly care physician [87, 89].

1.7. Purposes of nursing home care

The emphasis in Dutch nursing home care is not only on high quality medical and nursing care but in particular also on improving the quality of life (QOL) as experienced by the residents, by focusing on the individual preferences of the residents (person-centered care) and by creating an environment which offers an optimal balance between living, well-being and care [89-92]. A typical Dutch nursing home houses 150-200 residents but increasingly long term nursing home care facilities are "socialising" by changing into small scale facilities sited within larger nursing- and residential homes or in the community, supported by larger nursing homes [89-91].

Quality of life is multifaceted as is its measurement. Several QOL frameworks or approaches that focus on the entire older nursing home population exist. The QOL framework which is considered to be the most suitable as a basis for understanding and measuring the QOL in Dutch nursing home settings is the so called "Social Production Functions"-theory (SPF theory) [91]. In this theory, the basic assumption is that every individual wants to achieve overall subjective well-being by realising physical (stimulation/ activation; comfort) and social (status; behavioral confirmation; affection) well-being [92]. This assumption seems to be in accordance with the results of the anthropological section of the Dutch "Leiden 85-plus study on Successful Ageing" in which the perception of older people (inhabitants of the city Leiden, aged 85 year or older) of the concept of successful aging and the role of health in successful ageing, was investigated by conversations with 27 participants [93]. In this study, participants stated that successful ageing is equal to a feeling of well-being; to be satisfied with life, which appeared to be not necessarily linked to optimal health: scores on well-being do not change significantly if health declines. Older people redefine health as the maintenance of basic functioning and the absence of life-threatening disease and severe pain. Participants emphasise the individual responsibility to adapt to changes: adaptation was considered to be the essential element in successful ageing. In this study it was shown that, from the viewpoint of older people, there exists a hierarchy in domains for successful ageing. The most important domain was having social contacts. Participants stated that important conditions for life satisfaction are: to live in harmony with your environment; to be able to adapt to changes; not complaining; being together as a couple; being important for others; to have a good relationship with your children and seeing the children a lot [93].

Since 77% of the institutionalised older people are female, it is interesting that in addition to the findings in the Leiden 85-plus study, the American philosopher Sandra Lee Bartky, who unlike most classic philosophers, is reflecting on old age from the perspective of women, specifies the importance of social contacts: she argues that well-being in old age is also especially associated with affection, being found attractive and getting an adoring look [94, 95].
By focusing on improving the QOL of nursing home residents it is obvious that in defining person-centered nursing home care plans, the pursuit of well-being (with attention to the mentioned aspects) should always be a guiding principle. It is, given the high mortality in nursing homes, especially important that the desired treatment goals can be achieved within a realistic timeframe. Vitamin D supplementation is likely to meet these criteria and therefore one of the supposed basic elements in care plans for all nursing home residents [22].

1.8. In this thesis

The aim of this thesis is to gain knowledge concerning vitamin D supplementation in Dutch nursing home residents. The main focus will be on comparing different therapies to treat vitamin D deficiency. In ***chapter 2*** the effect of ultraviolet irradiation is compared

with oral vitamin D on the vitamin D status and parathyroid hormone concentration in a randomised clinical trial in 45 female nursing home residents. In ***chapter 3*** the feasibility and effectiveness of weekly, half body, full frontal ultraviolet B irradiation in obtaining vitamin D sufficiency is described in 8 nursing home residents. The effect of different doses and time intervals of oral vitamin D supplementation is compared in a randomised clinical trial in 338 nursing home residents and described in ***chapter 4***. In ***chapter 5*** the support for the vitamin D supplementation guidelines of the Health Council of the Netherlands by elderly care physicians is explored by a research survey and compared to that of general practitioners.
The prevalence of vitamin D deficiency in a special subgroup of younger than average nursing home residents, patients with Huntington's disease, is described in ***chapter 6***.
Finally in ***chapter 7*** together with methodological considerations the main findings of the studies included in this thesis are discussed as well as possible implications of the findings for clinical practice and future research.

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Chapter 2

Ultraviolet irradiation corrects vitamin D deficiency and suppresses secondary hyperparathyroidism in the elderly

V. G. M. Chel[1], M. E. Ooms[2], C. Popp-Snijders[3], S. Pavel[4], A. A. Schothorst[4], C. C. E. Meulemans[5], P. Lips[2,3]

(1) Psychogeriatric Centre Mariënhaven, Warmond, The Netherlands
(2) Institute for Research in Extramural Medicine, Vrije Universiteit, Amsterdam, The Netherlands
(3) Department of Endocrinology, Academic Hospital Vrije Universiteit, Amsterdam, The Netherlands
(4) Department of Dermatology, University Hospital Leiden, The Netherlands
(5) Optical Radiation Consultancy, Eersel, The Netherlands

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Abstract
The objective of this study was to compare the effect of ultraviolet radiation (UV) and oral vitamin D3 on the vitamin D status and parathyroid hormone (PTH) concentration in elderly nursing home patients. The design of the study was a randomised clinical trial. The setting was a psychogeriatric nursing home. Subjects included 45 female psychogeriatric patients with a mean age of 85 years. Exclusion criteria were going outdoors more than once a week and the presence of actinic or cancer skin lesions. Intervention was random allocation of UV-B irradiation at half the minimal erythemal dose of the lower back, three times per week during 12 weeks (UV-B), or oral vitamin D3 400 IU/day* during 12 weeks (VIT-D), or no treatment (CONTR). Main outcome measures were change in fasting serum levels of vitamin D metabolites at 0, 2, 4, 8, and 12 weeks in the treatment groups, compared with the control group. PTH(1–84) was measured at 0 and 12 weeks. Baseline serum 25-hydroxyvitamin D (25(OH)D) was lower than 30 nmol/l in 95% of the participants. It increased to a median value of around 60 nmol/l after 12 weeks both in the UV-B and VIT-D groups, whereas there was no change in the CONTR group. Serum 1,25-dihydroxyvitamin D increased significantly in the UV-B group. Serum calcium increased significantly in both treatment groups. Serum PTH decreased more than 30% in both treatment groups ($p < 0.001$), whereas there was no significant change in the control group. Irradiation with UV-B in the very elderly for a few minutes per day leads to adequate improvement of the vitamin D status. It is as effective as oral vitamin D3 in increasing serum 25(OH)D and suppressing secondary hyperparathyroidism.

* *According to the Dutch Nutrition Council in 1992 a daily intake of 100-200 IU cholecalciferol was considered to be adequate for older people. According to the most recent guidelines of the Dutch Health Council (2012) nowadays a daily supplementation of 800 IU is advised to people >70 years. See: 7.1.1.*

Introduction

Vitamin D deficiency is common in elderly people and in particular in patients with hip fracture [1]. It causes secondary hyperparathyroidism which leads to cortical bone loss [2, 3]. Vitamin D deficiency thus contributes to the pathogenesis of osteoporosis and hip fractures [4]. Vitamin D supplementation in the elderly increases the serum 25-hydroxyvitamin D (25(OH)D) concentration and decreases the serum concentration of parathyroid hormone (PTH) [5]. It also decreases wintertime bone loss from the lumbar spine [6] and it may increase bone mineral density of the femoral neck [7]. An annual intramuscular injection of vitamin D has been shown to decrease the incidence of upper limb fractures [8]. Low-dose vitamin D supplementation did not decrease the incidence of hip and other peripheral fractures in The Netherlands [9], whereas a combination of vitamin D and calcium decreased the number of hip fractures in elderly residents of nursing homes in France [10].

Elderly people do not often go outside in the sunshine [1]. The amount of ultraviolet (UV) light received by residents of homes for the elderly in The Netherlands has been found to be half that of people with an indoor occupation [11]. In addition, the production of vitamin D in the skin decreases considerably with aging. A study with UV radiation in Boston showed that the production of vitamin D3 at the age of 80 years is around 25% of that at the age of 20 years [12]. Sunshine exposure and consequently vitamin D3 production is particularly low in immobilised and institutionalised elderly people [13]. Earlier studies have demonstrated that sunlight exposure or UV irradiation could increase serum 25(OH)D in the elderly [14, 15]. The present study was undertaken to compare the effects of UV radiation and oral vitamin D supplementation on vitamin D deficiency and secondary hyperparathyroidism in elderly institutionalised people.

Subjects and methods

Subjects were 45 female patients of the nursing home Mariënhaven in Warmond (The Netherlands). All were residents from low and medium care psychogeriatric wards. Exclusion criteria were recent use of vitamin D supplementation and going outdoors more than once per week. The presence of actinic and cancer skin lesions as well as the skin type was checked by a dermatologist. All subjects had skin type 2 or 3. The dietary calcium intake of the subjects was ~1000 mg/day and the vitamin D intake was ~100 IU/day.

In The Netherlands, only margarine is fortified with vitamin D3 (3 IU/g). The diet does not contain vitamin D2. Written informed consent was obtained from proxies and treatment was discontinued when participants clearly objected or showed signs of discomfort. The protocol was approved by the Ethical Review Board of the Academic Hospital of the Vrije Universiteit. The participants were randomised in block to receive either ultraviolet B (UV-B) radiation or vitamin D3 or no treatment. The UV-B radiation was applied at an area of 1000 cm2 of the lower back, three times a week at half the individual minimal erythemal dose (MED). To optimise comfort, this was done in an adjustable chair. In the back of the chair, an opening of 1000 cm2 was covered with an acrylate plate. The UV-B source was placed

at a distance of 45 cm. The source consisted of three Philips TL12 (20 W) fluorescent tubes (Philips, Roosendaal, The Netherlands), protected by a UV-B transparent acrylate plate. The energy of UV-B at the skin was 17 mW/cm2. The output was measured with an International Light Radiometer (IL 700) connected to a SEE 400 sensor with a WBS 320 filter (International Light, Inc., Newburyport, MA, U.S.A.). Because only 67% of the measured radiation is in the UV-B range, all readings were multiplied by 0.67 to obtain the UV-B values. MED was determined using the same UV source and UV intensity as used for the treatment. Six areas of 4 cm2 were irradiated with UV-B doses increasing from 30 up to 140 mJ/cm2. The areas were subsequently inspected for erythema after 24 h. The irradiations were started following the baseline measurements. The other participants received either 400 IU of vitamin D3 (Devaron, Duphar, The Netherlands) in 1 tablet daily or no treatment. Fasting blood samples for biochemical measurements were obtained at baseline and after 2, 4, 8, and 12 weeks of treatment. An additional sample was obtained at 16 weeks, i.e., 4 weeks after treatment. Serum 25(OH)D was measured by radioimmunoassay with an intra-assay coefficient of variation (CV) of 8% (Nichols Diagnostics, San Juan Capistrano, CA, U.S.A.). Serum 1,25-dihydroxyvitamin D (1,25(OH)2D) was measured by radioreceptorassay following column extraction with an intra-assay CV of 7% (Incstar Corp., Stillwater, MN, U.S.A.). Serum PTH was measured by immunoradiometric assay (Medgenix Diagnostics, Fleurus, Belgium) at baseline and at 12 weeks. The intra-assay CV of this technique is 4%. Serum concentrations of sex hormone binding globulin (SHBG) were measured by immunoradiometric assay with an intra-assay CV of 5% (Farmos Diagnostics, Oulunsalo, Finland). For these biochemical parameters, the sera of a single participant were all measured within the same run to increase precision. Serum calcium, phosphate, albumin, and creatinin were measured using standard laboratory procedures. Serum calcium was corrected for serum albumin using the formula: corrected serum calcium (mmol/l) = serum calcium + (40-serum albumin [g/l]) × 0.02. Statistical analysis was performed using the PC version of the Statistical Package for the Social Sciences (SPSS-PC). The effect of treatment was defined as the difference between the mean changes of the biochemical parameters at week 12 (end of treatment) in either treatment group and the mean change in the control group. This was analysed using multiple linear regression, checking for normality and constancy of variance of the residuals. The difference between the groups in change of serum 25(OH)D at the various follow-up moments was analysed using analysis of variance for repeated measurements.

Results

The mean age of the patients was 85 years. Their MED values were in the normal range, varying from 40 to 140 mJ/cm2. The UV-B irradiations only took 3–7 minutes. No skin erythema or other complications were observed. Patient characteristics and baseline biochemical data are shown in table 1.

table 1. characteristics and biochemical parameters in serum of 45 participants at baseline by intervention group.

Variable	**UV-B** (n = 15) *Mean*	*SD*	**Vitamin D** (n - 15) *Mean*	*SD*	**Control** (n - 15) *Mean*	*SD*
Age (years)	84.2	7.4	84.4	6.3	85.3	5.2
Calcium (mmol/l)*	2.3	0.08	2.3	0.08	2.4	0.12
Phosphate (mmol/l)	1.02	0.12	1.01	0.14	1.04	0.18
SHBG (nmol/l)†	60.2	16.0	65.6	31.5	66.9	21.6
	Median	Percentiles	Median	Percentile	Median	Percentile
25(OH)D (nmol/l)	18	12, 25	23	14, 28	12	8, 18
1,25 $(OH)_2$D (pmol/l)	56	42, 67	68	44, 7.1	45	34, 68
PTH(1-84) (pmol/l)	6.2	4.8, 8.1	5.6	4.4 7.2	5.1	3.7 7.9
Creatinine (цmol/l)	80	75, 100	82	70, 92	83	70, 94

* corrected for serum albumin
† serum sex-hormone binding globulin
For skewed variables, median values 25th and 75th percentiles are given

Most participants, i.e., 42 out of 45, were vitamin D deficient (serum 25(OH)D < 30 nmol/l) and about 60% were severely vitamin D deficient (serum 25(OH)D < 20 nmol/l). The mean serum PTH was increased in the participants compared with values obtained in young adults (reference value 1.1–6.3 pmol/l). There was no significant correlation between baseline serum PTH and serum 25(OH)D. There was a strong positive correlation between the baseline serum concentrations of 25(OH)D and 1,25(OH)2D ($r = 0.39$, $p < 0.001$). The treatment period of 12 weeks was completed by 11 patients in the UV-B group, 14 in the vitamin D group, and 14 in the control group. In all groups, one patient had died and in the UV-B group three patients had refused further participation.
The course during the study period of serum 25(OH)D in the various treatment groups is shown in fig. 1.
According to analysis of variance for repeated measurements, the increase in both treatment groups was highly significant when compared with the control group (both $p < 0.001$). The increase in serum 25(OH)D after 2 weeks was 11 nmol/l in the UV-B group and 15 nmol/l in the vitamin D group, both significantly different from the 1 nmol/l decrease in the control group ($p < 0.001$). After 12 weeks, the median serum 25(OH)D was 60 nmol/l in both treatment groups ($p < 0.001$). Nonresponders to UV-B or oral treatment were not observed. At week 16, i.e., 4 weeks after discontinuing treatment, serum 25(OH)D had decreased by 16 nmol/l in the UV-B group and 10 nmol/l in the vitamin D group, which was in both groups significantly different from the change in the control group (all $p < 0.001$).
In Table 2, the changes in the biochemical parameters due to the interventions are given. Serum 1,25(OH)2D increased significantly in the UV-B group. Serum calcium showed a

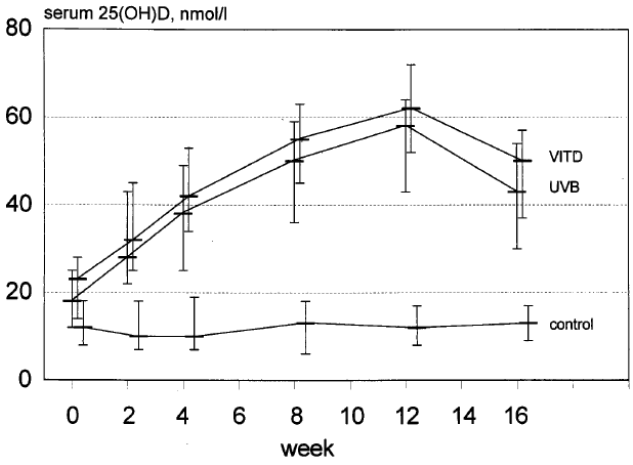

figure 1. Serum 25(OH)D (median, 25th -75th percentile) in elderly women treated during12 weeks with 400IU of oral vitamin D (vit D, $p < 0{,}001$) or irradiation of the skin with UV light (UV-B, $p < 0{,}001$) and in the control group.

table 2. Mean change (Δ)from baseline to the end of the intervention period in biochemical parameters in serum by intervention group

	UV-B *(n = 11)*			**Vitamin D** *(n = 14)*			**Control** *(n = 14)*	
Variable	Δ	SD	p*	Δ	SD	p*	Δ	SD
1,25 (OH)2D (pmol/l)	11.2	17.1	0.02	–4.0	14.6	0.80	–2.9	10.1
Calcium (mmol/l)†	0.079	0.057	0.01	0.076	0.047	0.01	0.024	0.058
Phosphate (mmol/l)	–0.03	0.14	0.45	0.07	0.18	0.39	0.02	0.14
PTH(1-84) (pmol.l)	–2.2	1.6	0.0002	–2.1	1.1	0.0002	–0.1	1.2
Creatinine (цmol/l)	0.2	10.7	0.95	0.4	11.1	0.90	–0.1	9.6

*p value when compared with control group
† corrected for serum albumin

significant increase in both treatment groups. Serum PTH decreased by 2.2 pmol/l in the UV-B group and 2.1 pmol/l in the vitamin D group ($p < 0.001$), whereas there was little change (−0.1 pmol/l) in the control group (Fig. 2). The effect of treatment on serum PTH was dependent on the serum concentration of SHBG ($p = 0.08$), i.e., serum PTH decreased more when serum SHBG was higher.

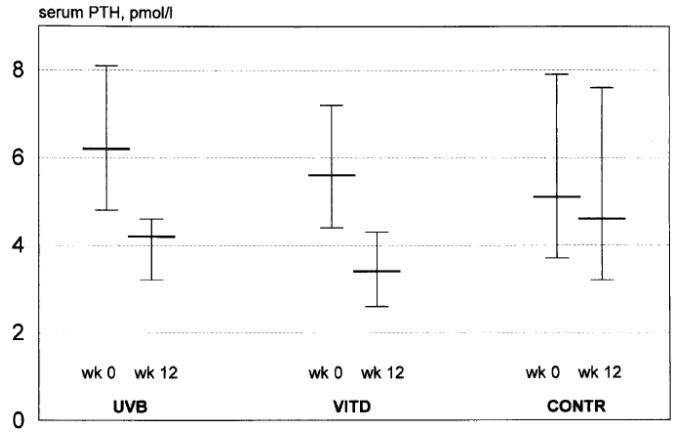

figure 2. Serum PTH (median, 25th -75th percentile) in elderly women at baseline (week 0) and after 12 weeks (week12) of treatment with 400IU of oral vitamin D (vit D, $p < 0{,}0002$) or irradiation of the skin with UV light (UV-B, $p < 0{,}0002$) and in the control group.

Discussion

The results of this study confirm the poor vitamin D status usually observed in institutionalised elderly. Serum 25(OH)D was even lower in these psychogeriatric patients than in institutionalised elderly in The Netherlands, resulting in median serum PTH levels in the upper normal range [1, 13]. A negative correlation between serum PTH and serum 25(OH)D was not observed, probably because serum 25(OH)D concentrations were all very low in the patients. The strong positive relation of serum 25(OH)D with serum 1,25(OH)2D suggests that the production of the latter is substrate dependent in these very vitamin D-deficient elderly patients, as has been observed in other studies [1, 16].

The treatment with UV-B resulted in a steady, almost linear, increase of serum 25(OH) D, which was very similar to the effects of oral vitamin D3. It has been observed that the production of vitamin D3 in the skin following UV-B irradiation at the age of 80 years is around 25% of that at the age of 20 years [12]. The present study shows that the aged skin still has an adequate capacity to produce vitamin D3 following intense UV-B irradiation of short duration. An earlier study in long-stay geriatric patients showed effects of irradiation during 3 h/day on 4000 cm2 of skin. In that study, serum 25(OH)D increased 30 nmol/l in 8 weeks [14]. The much smaller skin area and the much shorter irradiation time per session that we needed to obtain similar results may be explained by the fact that we adjusted the individual dose to the sensitivity of the skin as determined by the MED and the intensity was higher.

The decrease of serum PTH was more than 30% in both treatment groups. This is a larger decrease than that observed in our previous vitamin D supplementation study in healthy elderly women, where the decrease of serum PTH was 15% [7]. This is consistent with the

greater degree of secondary hyperparathyroidism and more severe vitamin D deficiency observed in these psychogeriatric patients. Moreover, serum 1,25(OH)2D and serum calcium increased, indicating severe deficiency. The effect of treatment on serum PTH was greater when serum SHBG was higher, i.e., when free estrogen levels were lower. In our previous studies, we observed more severe secondary hyperparathyroidism and a greater increase in bone mineral density following vitamin D supplementation when SHBG was high [7, 17]. The suppression of PTH secretion may substantially reduce bone turnover and bone loss, although this was not the subject of this study. We conclude that regular exposure of short duration to UV-B can correct vitamin D deficiency and secondary hyperparathyroidism without serious side effects in very elderly nursing home residents. The effects of UV-B are similar to those of oral supplementation with 400 IU of vitamin D3 per day.

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Chapter 3

Prevention and treatment of vitamin D deficiency in Dutch psychogeriatric nursing home residents by weekly half body UV-B exposure after showering: a pilot study

V.G.M. Chel[1, 2], M.E Ooms[2], S. Pavel[3], F. de Gruijl[3], A. Brand[4], P. Lips[2, 5]

(1) Topaz location Overduin Katwijk, The Netherlands
(2) EMGO Institute, VU University Medical Center, Amsterdam, The Netherlands
(3) Department of Dermatology, Leiden University Medical Centre, Leiden, The Netherlands
(4) European Sunlight Association / Samenwerking Verantwoord Zonnen
(5) Department of Endocrinology, VU University Medical Center, Amsterdam, The Netherlands

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Abstract

background: In older people, induction of cutaneous vitamin D production by ultraviolet B (UV-B) exposure may be preferable to oral supplementation: it cannot cause toxic levels, it helps to prevent polypharmacy and, moreover, there are indications that UV-B exposure has beneficial effects on health and well-being by mechanisms other than the vitamin D pathway alone.
objective: The aim of this pilot study is to investigate whether weekly, half body, UV-B irradiation after showering can increase serum 25-hydroxyvitamin D (25(OH)D) to sufficient levels, in a Dutch psychogeriatric nursing home population.
method: Subjects were 8 psychogeriatric nursing home patients, mean age: 79 ± 8. Exclusion criteria were going outdoors into the sun more than once a week, the presence of actinic or cancer skin lesions and known resistance to body contact. The intervention consisted of weekly half-body UV-B irradiation, after showering, over 8 weeks, with 0.5 minimal erythemal dose (MED). Main outcome measures were change in fasting serum levels of 25(OH)D and PTH at 0, 2, 4 and 8 weeks.
results: At baseline, mean serum 25(OH)D was 28.5 nmol/L. Mean serum 25(OH)D levels increased to 46.5 nmol/L. Median serum PTH levels decreased by 20% after 8 weeks of treatment.
conclusion: An eight week course of weekly, frontal half body irradiation with UV-B, at 0.5 MED, leads to an significant increase in 25(OH)D serum levels, but this period is too short to reach vitamin D sufficiency.

Introduction

Vitamin D deficiency (25(OH)D < 25 nmol/L) and vitamin D insufficiency (25(OH)D < 50 nmol/L) is common in older people, in particular in nursing home residents [1, 2]. Vitamin D deficiency causes secondary hyperparathyroidism, which leads to cortical bone loss [3]. It may also lead to fatigue, muscle weakness and falls [4, 5]. Vitamin D deficiency thus contributes to the pathogenesis of osteoporosis and fractures.

However, the vitamin D receptor has been found in many other tissues and vitamin D deficiency is associated with multiple health problems such as increased risk of common cancers, autoimmune diseases, hypertension, knee cartilage loss, pain, cognitive impairment and depression [6-11].

In humans and most other species the most important way for obtaining an adequate vitamin D status is sunlight (UV-B part) exposure [12]. In nursing home residents in particular, the most common cause of vitamin D deficiency is not going outside in the sun. The production of vitamin D_3 at the age of 80 (aged skin), is around 25% of that of the age of 20 [13]. Nevertheless in older nursing home residents, 3 times a week artificial UV-B irradiation, on a limited area of the skin, proved to be equally effective as oral vitamin D supplementation, in correcting vitamin D deficiency [14].

Induction of cutaneous Vitamin D production by UV-B exposure may be preferable to oral supplementation in older nursing home residents, because it cannot induce toxic levels; the use of UV-B lamps is a feasible and economic alternative for sunshine exposure and has the additional benefit that it can provide cutaneous vitamin D synthesis throughout the year; it helps in preventing polypharmacy and it is plausible that vitamin D production is not the only pathway whereby sunlight or UV-B exposure has beneficial effects on human health and well-being [15].

In order to investigate, in a larger follow up study, whether artificial UV-B exposure has an additional value on quality of life of older nursing home residents in correcting vitamin D deficiency, the aim of this smaller pilot study is to investigate whether, in a Dutch psycho-geriatric nursing home population, half body, full frontal UV-B irradiation, only once a week, after showering, is feasible and effective in obtaining vitamin D sufficiency (serum 25(OH)D > 50 nmol/L).

Subjects and methods

Subjects were 5 female and 3 male residents of low and medium care wards of the psychogeriatric nursing home Mariënhaven in Warmond (The Netherlands / latitude: 52°N) with a mean age of 79 (71-87). Exclusion criteria were going outdoors into the sun more than once a week; the use of vitamin D supplements; the presence of actinic or cancer skin lesions and known anxiety, agitation or resistance to body contact. The presence of actinic or cancer skin lesions as well as the skin type was checked by a dermatologist. All subjects had skin type 2 or 3. The estimation of the skin type was based on the skin and eye colour of the participants and on the recollection of their relatives as regarded the sun exposure of the participants [16].The dietary vitamin D intake of this population was approximately

100 IU/day and the calcium intake was approximately 1000 mg/day [2, 17]. Written informed consent was obtained from proxies and treatment was discontinued when participants clearly objected or showed signs of discomfort. The protocol was approved by the Ethical Review Board of the VU University Medical Centre Amsterdam. Once a week, over a period of 8 weeks, after showering, all participants received UV-B irradiation at 1.0 Standard Erythema Dose (SED) = a CIE (Comite International de l' Eclairage) dose of 100 J/ m2 = 50% of the Minimal Erythema Dose (MED) for skin type 2 (2 minutes at 1 m distance from the UV-B lamps). UV-B irradiation took place while seated in a standard, comfortable, electrically adjustable, Carendo® bathroom chair; the same chair in which the participants were showered. For the UV-B irradiation, an obliquely installed Hapro® sunbed was used with 2 Philips® 100W/12 (high UV-B intensity) and 8 Philips® Cleo sunbed TL lamps. Before first use, the sunbeds were tested at the dermatology department of the Leiden University Medical Centre. During the UV-B irradiation the eyes of the participants were protected. Fasting blood samples were taken at 0, 2, 4 and 8 weeks. Samples were processed within 2 hours after drawing and serum was stored at minus 23°C. Serum 25(OH) was measured by radioimmunoassay (Diasorin, Stillwater, MN) with an inter-assay coefficient of variation (CV) of 10% at 30 nmol/L. Serum PTH was measured by radioimmunoassay (Incstar, San Juan Capistrano, CA) with an inter-assay CV of 10% at 3,5 pmol/L. For these parameters the sera of a single participant were all measured within the same run to decrease variation. Analyses were done in duplicate. The VUmc laboratory adheres to quality assessment schemes (DEQAS and SKML). Serum calcium, phosphate, albumin, creatinine and alkaline phosphatase (APh) were measured using standard laboratory procedures, immediately after obtaining the blood samples.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0. The effect of treatment was tested by using paired t-tests on the serum levels at week 0 versus week 8. $p<0,5$ was considered statistical significant.

Results

The mean age of the participants was 79 ±8 years. No skin erythema or other complications developed during the study. All but one of the participants were vitamin D insufficient (serum 25(OH)D < 50 nmol/L) at t0. Serum levels of 25(OH)D and PTH in each individual during the study period are shown in figure 1 and figure 2. Serum levels of calcium, during the study period are shown in figures 1 and 2.

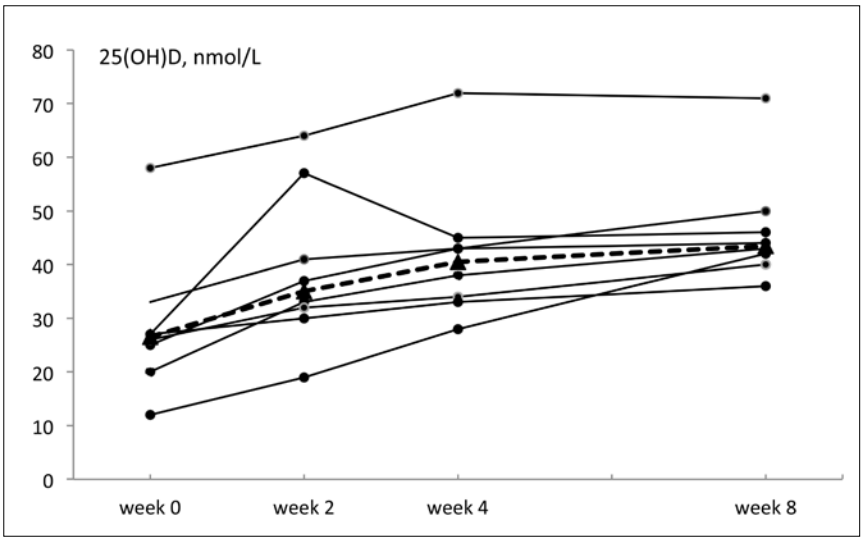

figure 1. Serum 25(OH)D levels in individual participants at each follow up moment. The dotted line represents the median values.

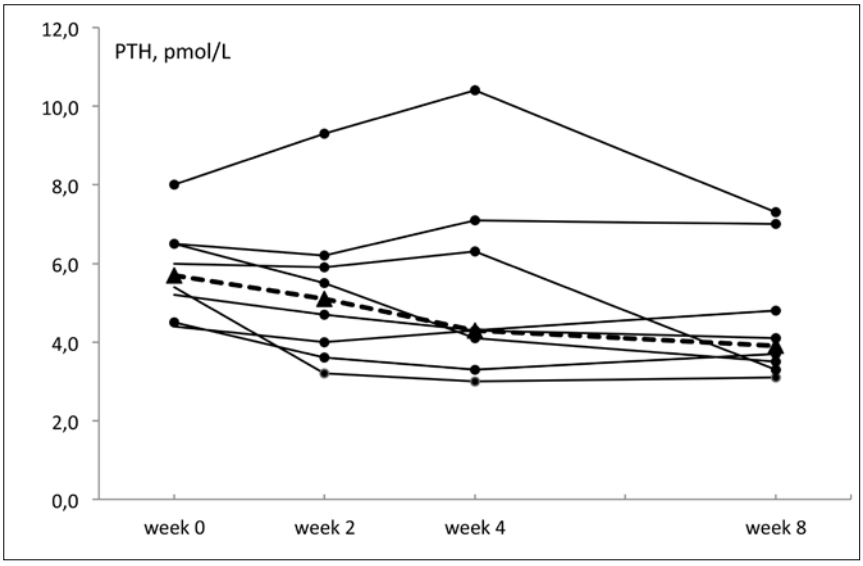

figure 2. Serum PTH levels in individual participants at each follow up moment.The dotted line represents the median values.

Serum levels of calcium, albumin, alkaline phosphatase, phosphate and creatinine are shown in table 1.

table 1. mean, standard deviation (SD) and median for biochemical parameters in blood at baseline (week 0) and after 8 weeks

serum concentration	refs	week 0			week 8		
		mean	SD	median	mean	SD	median
calcium (corrected), mmol/L	2.25-2.55	2.44	0.06	2.42	2.49	0.08	2.48
albumin, g/L	40-50	34.63	2.82	34.50	32.38	3.85	31.00
phosphate, mmol/L	0.81-1.45	1.06	0.10	1.06	1.14	0.11	1.15
alk. phosphatase, U/L	40-120	83.25	18.08	86.00	84.75	20.56	89.00
creatinine, µmol/L	70-133	79.88	14.23	78.00	80.75	19.45	78.50

Serum 25(OH)D increased in all individuals and the median serum 25(OH)D increased from 26.5 nmol/L (12-58) at baseline (t0) tot 43.5 nmol/L (36-71) after eight weeks (t3) ($p<0.001$).
Although the median serum PTH at baseline was not increased in most participants compared with values obtained in young adults (reference value 1.1 – 6.3 pmol/L), it decreased from 5.7 pmol/L (4.4-8.0) at t0 to 3.9 pmol/L (3.1-7.3) at t3 ($p=0.03$).

Discussion

The results of this pilot study confirm the poor vitamin D status usually observed in nursing home residents. In all participants serum 25(OH)D levels increased with UV-B exposure, vitamin D sufficiency however was not reached in most subjects. Because serum 25(OH) D levels continued to increase during the study period it is to be expected that vitamin D sufficiency can be reached with the same UV-B exposure over a longer period or with UV-B exposure at 90% MED (by increasing the exposure time per session or by using more high intensity UV-B lamps). The nursing staff reported that the weekly UV-B irradiations were appreciated by the participants and easy to perform.
In this pilot study UV-B exposure was full frontal, at 0.5 MED once a week after showering. In an earlier study, also in a Dutch psychogeriatric nursing home, the effect of UV-B exposure applied at an area of 1000 cm2 of the lower back, three times a week at half the individual MED, was compared with oral vitamin D3 400 IU/day. Baseline serum 25(OH) D was lower than 30nmol/L in 95% of the participants in the previous study and increased to a median value of around 60 nmol/L after 12 weeks. Serum PTH decreased more than 30%. The administered UV-B exposure was as effective as the oral dose given, both in increasing serum 25(OH)D and suppressing secondary hyperparathyroidism [14].
Although oral vitamin D3 supplementation is effective and easy to perform, induction of cutaneous vitamin D production by UV-B exposure can be equally effective and possibly has additional health benefits. The beneficial role for UV-B on some auto-immune

diseases (multiple sclerosis; insulin-dependent diabetes mellitus and rheumatoid arthritis) is linked to suppression of T helper cell type 1 mediated immune responses, possibly through several other mechanisms apart from vitamin D effects (i.e apart from other pathways, UV radiation has a direct immunosuppressive effect. UV-B possibly can up-regulate secretion of TNF-alpha, IL-10 and T regulatory cells, providing both local and systemic immunosuppression) [15, 18-21]. Although UV exposure is considered to be the major cause of skin cancer, in several studies an inverse correlation was found between sunlight and mortality or incidence of colorectal, prostate, breast and ovary cancer and it was questioned whether vitamin D synthesis is the only mechanism by which sunlight exerts its possible preventive effect on these cancers [15, 21-25]. Going outside into the sun and obtaining a tan, rightly or wrongly, is generally associated with a feeling of well-being and good health [21-23, 25]. Especially in older nursing home residents this perceived feeling of good health is likely to be combined with a more active social life as a result of leaving the nursing home more often and may have an important effect on the quality of life in this frail population.

We conclude that UV-B exposure, at 0.5 MED, once a week, of the frontal half of the body, after showering, leads to an important improvement of the vitamin D status in older nursing home residents. Eight weeks however, were not enough to reach vitamin D sufficiency.

We will now carry out a follow up study, to investigate whether weekly UV-B exposure throughout the year, has an added value on quality of life of elderly nursing home residents in correcting vitamin D deficiency compared to oral vitamin D supplementation.

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Chapter 4

Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents

V. Chel,[1,2] H.A.H. Wijnhoven,[2] J. Smit,[3], M. Ooms[2], P. Lips[2,4]

(1) Verpleeghuis Marienhaven, Warmond, The Netherlands
(2) EMGO Institute, VU University Medical Center, Amsterdam, The Netherlands
(3) Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands
(4) Department of Endocrinology, VU University Medical Center, Amsterdam, The Netherlands

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Abstract

summary: The effect of equivalent oral doses of vitamin D3 600 IU/day, 4200 IU/week and 18,000 IU/month on vitamin D status was compared in a randomised clinical trial in nursing home residents. A daily dose was more effective than a weekly dose, and a monthly dose was the least effective.

introduction: It is assumed that equivalent daily, weekly or monthly doses of vitamin D3 equally influence vitamin D status. This was investigated in a randomised clinical trial in nursing home residents.

methods: The study was performed in ten nursing homes including 338 subjects (76 male and 262 female), with a mean age of 84 (± SD 6.2 years). They received oral vitamin D3 either 600 IU/day*, 4200 IU/week, 18,000 IU/month or placebo. After 4 months, calcium was added during 2 weeks, 320 mg/day, 640 mg/day, or placebo. Outcome: serum levels of 25-hydroxyvitamin D (25(OH)D), parathyroid hormone (PTH) and bone turnover markers. Statistical approach: linear multilevel analysis.

results: At baseline, mean serum 25(OH)D was 25.0 nmol/L (SD 10.9), and in 98%, it was lower than 50 nmol/L. After 4 months, mean serum 25(OH)D levels increased to 62.5 nmol/L (after daily vitamin D3 69.9 nmol/L, weekly 67.2 nmol/L and monthly 53.1 nmol/L, < 0.001 between groups). Median serum PTH levels decreased by 23% (< 0.001). Bone turnover markers did not decrease. Calcium supplementation had no effect on serum PTH and bone turnover.

conclusion: Daily vitamin D was more effective than weekly, and monthly administration was the least effective.

* *According to the Dutch Health Council in 2000 a daily intake of 600 IU cholecalciferol was considered to be adequate for people > 70 years. According to the most recent guidelines of the Dutch Health Council (2012) nowadays a daily supplementation of 800 IU is advised to people >70 years. See:7.1.3.*

Introduction

Vitamin D deficiency is common in older persons, in particular in residents of homes for the elderly and nursing homes and in patients with hip fracture [1–3]. In these groups the prevalence of vitamin D deficiency, defined at that time as serum 25(OH) D <30 nmol/L based on values in healthy blood donors, was reported to be 75% [3]. This is mainly explained by the fact that older persons do not often go outside in the sunshine and dietary vitamin D intake is low. Vitamin D deficiency causes secondary hyperparathyroidism, which leads to cortical bone loss, osteoporosis and fractures [4]. It may also cause fatigue, muscle weakness, increased body sway and falls [5, 6]. Vitamin D supplementation in vitamin D deficient elderly increases the serum concentration of 25-hydroxyvitamin D (25(OH)D) and decreases the serum concentration of parathyroid hormone (PTH) [3]. It also decreases wintertime bone loss from the lumbar spine [7] and increases bone mineral density of the femoral neck [8]. Vitamin D supplementation combined with calcium decreased body sway and falls in a German study [5] and decreased hip as well as other non-vertebral fractures in French nursing home residents [9], whereas the results in more healthy elderly, living independently in the community were equivocal [10–14].

Vitamin D status in the elderly may be improved by ultraviolet irradiation [15] or by vitamin D supplementation [3, 7, 8–14]. Some controversy exists on the required serum 25(OH)D level, but most investigators agree that the level should be at least 50 or even 75 nmol/l [16, 17]. The Dutch Health Council advises vitamin D 600 IU daily for elderly of 70 years and older who do not come outside in the sunshine [18]. Oral vitamin D3 can be taken once a day but also with longer intervals because of its long half-life, being around 25 days. It is not known whether equivalent doses once a week or once a month are equally effective.

A low calcium intake aggravates vitamin D deficiency by increasing the turnover of vitamin D metabolites by secondary hyperparathyroidism [4]. On the other side, a high calcium intake does not completely protect against secondary hyperparathyroidism, and thus cannot compensate for vitamin D insufficiency [19]. The calcium requirement for skeletal maintenance is raising with age whereas the capacity for compensating a low calcium intake declines with age [20]. In the Netherlands the mean daily calcium intake of independently living elderly in homes and apartments of the elderly is about 900 mg [2]. In the guidelines of the Dutch Health Council, the advised daily amount of calcium for elderly 70 years and older is 1200 mg [18].

The aim of the present study was to investigate, in a Dutch nursing home population, whether there is a difference in efficacy of different doses and intervals of oral vitamin D3 supplementation with the same total dose. A second aim was to assess the additional effect of calcium supplementation following vitamin D supplementation on serum PTH and markers of bone turnover.

Subjects and methods

Subjects

Ten somatic and psychogeriatric nursing homes participated and 1,006 subjects were invited. Of these, 146 did not respond, 386 refused to participate and 136 did not meet inclusion criteria. Participants were 338 (76 male and 262 female) patients of 70 years or older with a mean age of 84 years (SD 6.2). Exclusion criteria were going outside in the sunshine more than once a week, the use of vitamin D or calcium supplementation, the use of more than one vitamin D-fortified food or drink per day, complete immobilisation and a very poor life expectancy. Poor cognition was not an exclusion criterion. This did not affect adherence. Nursing homes were enrolled in the study throughout the year. Participants living together in the same nursing home started the study during the same season. The dietary vitamin D intake was estimated at about 100 IU/day, based on fish and margarine consumption. In the Netherlands only margarine is fortified with vitamin D3 (3 IU/g) and the diet does not contain vitamin D2. Written informed consent was obtained from participants or their proxies. The protocol as well as the patient information letters were approved by the Ethical Review Board of the VU University medical center.

Randomisation

Participants were randomised in blocks of six, to receive, during the study period of four and a half months, either oral vitamin D3 600 IU/day (one tablet) or placebo, 4200 IU/ week (seven tablets once a week) or placebo or 18,000 IU/month (one powder once a month) or placebo. (Solvay Pharmaceuticals, Weesp, Netherlands). After four months, participants in every group were randomised again to receive during 14 days either calcium carbonate or placebo. The first 156 participants who were randomised received 800 mg calcium carbonate (320 mg Ca2+) or placebo, the subsequent 120 participants received 1,600 mg calcium carbonate (640 mg Ca2+) or placebo. The study medication was centrally distributed to ensure compliance. The study was completed by 269 patients.

Measurements

At baseline co-medication was registered and a questionnaire for dietary calcium intake was used to calculate the mean daily calcium intake from dairy products, underestimating calcium intake by 200–300 mg/day [2, 21].

The ability of standing and walking was assessed by a standing score, ranging from 1 (cannot stand alone) to 5 (can easily get up and remain standing without help) and a walking score ranging from 1 (cannot do one active step) to 5 (completely independent walking). Both scores have previously been described [22].

During the study all falls and fractures were registered by the nursing staff on special forms and checked with the routine incident registration. At the end of each study period in a nursing home, every ward was asked to complete a questionnaire on the opinion of the nursing staff about the suitability of each distribution form, compliance, the risk of making mistakes, time investment and preferences.

Random samples of the returned medication were counted in order to verify compliance. Adequate compliance was defined to exist when more than 80% of the study medication was ingested. Twice a quality check was made on the research medication by taking random samples for determining the vitamin D3 content of tablets and powders. Fasting blood samples were obtained at baseline, at two and four months.
Serum 25(OH)D was measured by radioimmunoassay (Diasorin, Stillwater, MN) with an inter-assay coefficient of variation (CV) of 10% at 30 nmol/L. Serum PTH was measured by radioimmunoassay (Incstar, San Juan Capistrano, CA) with an inter-assay CV of 10% at 3.5 pmol/L. Serum carboxy-terminal collagen crosslinks or CTX, a marker for bone resorption, was measured by immuno-assay (CrossLaps, (Roche) with an interassay CV of 5%.
For these parameters the sera of a single participant were all measured within the same run to decrease variation. Serum calcium, phosphate, albumin, creatinine and alkaline phosphatase (APh) were measured using standard laboratory procedures, immediately after obtaining the blood samples. Serum calcium was corrected for serum albumin using the formula: *corrected calcium (mmol/L)= measured [calcium] + (40 – albumin (g/L) x 0.02*

Statistical analysis
Statistical analysis was performed using SPSS 12.0.1. Data are presented as means (and standard deviation [SD]) or – in case of skewed distributions – as medians (and interquartile range [IQR]). Associations between baseline serum 25(OH)D and PTH, PTH and AF, and AF and CTX were examined by means of the Pearson correlation coefficient or – when one or both outcome variables had a skewed distribution – the Spearman rank order correlation coefficient. Baseline characteristics of dropouts and completers were compared by logistic regression analysis. Linear multilevel analysis with SPSS Mixed Models was used to investigate: (1) the effect of vitamin D supplementation on change (from baseline (t0) to 4 months (t2)) in biochemical outcome variables (serum 25(OH)D, serum PTH, bone turnover markers) and (2) the effect of additional calcium supplementation on change (from 4 months (t2) to 4.5 months (t3)) in biochemical outcome variables, adjusting for possible clustering of observations. The included levels were repeated measures (i.e., time), respondent, and nursing home. Nursing home was included in the final analyses only in case of a change of the effect size of more than 10%. Separate models were created with 25(OH)D, phosphate, corrected calcium, CTX, PTH, and APh as the respective dependent variables. We examined the potential confounding effect of season, age, sex, mean daily calcium intake, creatinine, standing and walking score at t0. For PTH and APh, logarithmic transformations were performed to normalise variance to allow parametric tests. For these log-transformed outcome variables, the estimated mean difference between two intervention groups was transformed back using an antilog transformation. The resulting estimate is the ratio of the geometric means of the outcome variable in both intervention groups. The geometric mean resembles the median. The level of significance was set at $P<0.05$.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the 338 participants enrolled in the study. These were very similar for the different intervention groups.

table 1. Characteristics of 338 participants at baseline (t_0) by intervention group at t_0 (Pl D = placebo vitamine D, D = vitamin D) and t_2 (Pl Ca = placebo calcium, Ca = calcium)

	Total (n=338)	D total (n=166)	D daily (n = 55)	D weeky (n=54)	D monthly (n = 57)	Pl D total (n = 172)	Ca[b] (n = 68)	Pl Ca[b] (n = 71)
% female	77.5	76.5	83.6	72.2	73.7	78.5	76.5	78.9
Variable	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Age (yr)	84.2 (6.2)	84.2 (6.5)	84.3 (6.3)	84.3 (6.4)	83.9 (6.9)	84.2 (5.9)	83.3 (6.2)	84.5 (6.8)
25(OH)D (nmol/L)	25.0 (10.9)	24.9 (10.1)	24.0 (8.6)	26.7 (12.6)	24.1 (8.8)	25.0 (11.7)	25.3 (10.6)	24.1 (9.6)
Calcium corrected (mmol/L)	2.42 (0.10)	2.42 (0.09)	2.42 (0.09)	2.41 (0.08)	2.42 (0.10)	2.43 (0.10)	2.41 (0.08)	2.42 (0.10)
Phosphate (mmol/L)	1.03 (0.14)	1.02 (0.14)	1.02 (0.13)	1.02 (0.16)	1.02 (0.13)	1.04 (0.14)	1.01 (0.14)	1.03 (0.13)
CTX	592 (277)	571 (274)	594 (274)	626 (311)	496 (218)	613 (280)	552 (288)	565 (255)
Albumin (g/L)	33.4 (3.3)	33.4 (3.3)	33.0 (3.5)	33.1 (3.4)	34.2 (2.8)	33.4 (3.2)	34.0 (3.2)	33.0 (3.4)
Standing score (1-5)	3.3 (1.6)	3.3 (1.6)	3.5 (1.6)	3.1 (1.7)	3.5 (1.6)	3.3 (1.6)	3.2 (1.7)	3.5 (1.6)
Walking score (1-5)	3.0 (1.4)	3.0 (1.4)	3.0 (1.4)	3.0 (1.6)	3.0 (1.3)	3.0 (1.4)	2.9 (1.4)	3.1 (1.4)
Skewed variable	median (IQR)	median (IQR)	median (IQR)	median (IQR)	median (IQR)	median (IQR)	median (IQR)	median (IQR)
Calcium intake (mg/day)[a]	750 (560-1035)	750 (594-1015)	725 (623-1039)	755 (550-1028)	788 (583-955)	750 (550-1053)	773 (614-1024)	730 (565-1003)
PTH (pmol/L)	7.2 (5.1-10.5)	7.2 (5.2-10.4)	7.4 (5.2-10.4)	6.7 (5.3-9.9)	7.2 (5.1-10.5)	7.1 (5.1-11.1)	6.5 (5.2-9.4)	7.3 (5.1-10.9)
AF (U/L)	85 (69-102)	86 (71-104)	82 (73-100)	90 (68-106)	87 (67-105)	85 (69-99)	89 (68-105)	82 (67-98)
Creatinine (μmol/L)	93 (81-103)	92 (81-103)	87 (80-95)	96 (85-104)	94 (81-105)	93 (82-105)	91 (80-102)	92 (81-102)

IQR = interquartile range

[a] From dairy products

[b] Within participants completing the vitamin D intervention (n = 276) treated with vitamin D (n = 139)

In the total group, baseline mean serum 25(OH)D was 25.0 nmol/L (SD 10.9). In 55% of the participants, serum 25(OH)D was lower than 25 nmol/L while 77% had levels below 30 nmol/L and 98% below 50 nmol/L (data not shown). Baseline median serum PTH was 7.2 pmol/L (IQR 5.1–10.5) (ref. values: 1–11 pmol/L).

There were statistically significant correlations at baseline between serum 25(OH)D and serum PTH values (r = −0.25; *P* < 0.001), serum PTH and serum APh values (r = 0.16; *P* < 0.01), and serum APh and serum CTX values (r = 0.23; *P* < 0.001) (data not shown). The median daily calcium intake from dairy products was 750 mg (IQR 560–1035).

Trial schedule

Figure 1 shows the trial schedule as well as the results of the randomisation procedure of both the vitamin D and the calcium intervention. Of the 341 participants originally enrolled, three were enrolled incorrectly because of hypercalcemia (corrected serum calcium: 2.69; 2.83; and 2.85), leaving 338 participants eligible for the study.

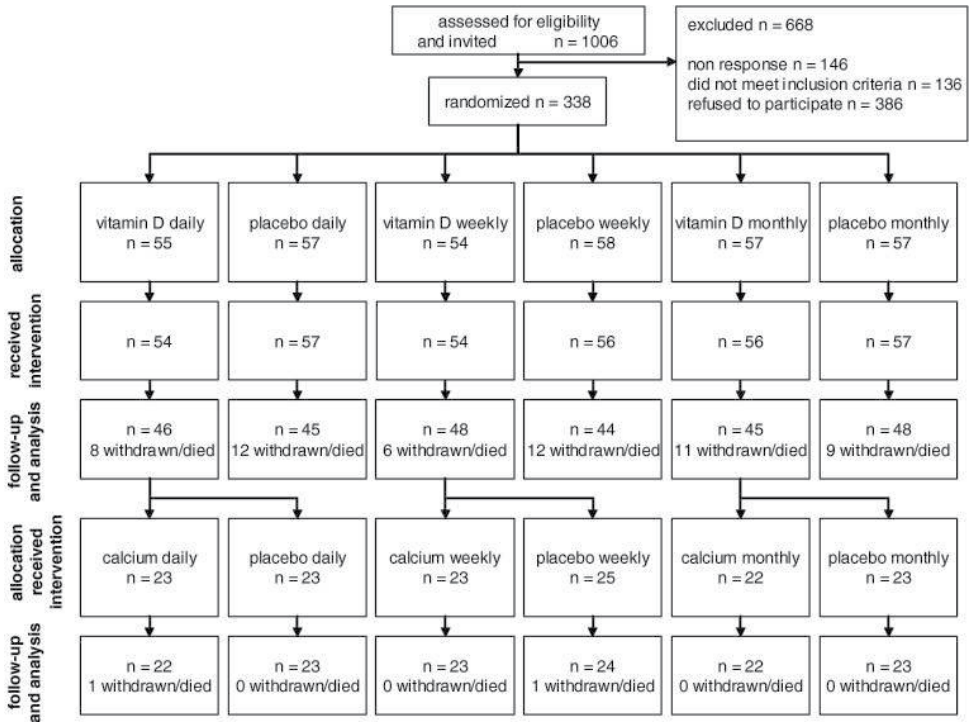

figure 1. Flow diagram of progress through the randomised clinical trial of vitamin D supplementation followed by the randomised clinical trial of calcium supplementation

Vitamin D intervention

The 338 enrolled participants were randomised to treatment with vitamin D3 one tablet of 600 IU each day (*n* = 55), a placebo in the form of one tablet each day (*n* = 57), vitamin D3 in the form of seven tablets (4200 IU) once a week (*n* = 54), a placebo in the form of seven tablets once a week (*n* = 58), vitamin D3 in the form of one powder (1,800 IU) once

a month (*n* = 57), or a placebo in the form of one powder once a month (*n* = 57). The treatment period of four months was completed by 276 participants. Of the 62 drop-outs, 41 died during the study period and there were 21 withdrawals: nine participants became terminally ill; five participants became uncooperative to donate a blood sample; one participant showed signs of discomfort during blood sampling; one participant became immobile; 3 participants were moved elsewhere; and one participant dropped out for unknown reasons. Finally, one participant was excluded from the analyses due to extremely high levels of alkaline phosphatase (278, 1025, 2661 U/L at, respectively, t_0, t_1, t_2) for unknown reasons (further analysis was refused by the patient). The number of drop-outs did not differ significantly between the placebo (*n* = 35) and the vitamin D group (*n* = 27). Dropouts were similar to completers with respect to most baseline characteristics (sex, age, 25(OH)D, corrected calcium, phosphate, albumin, standing score, walking score, mean daily calcium intake, and creatinine), but had higher serum levels of CTX, and APh ($P < 0.05$) (data not shown).

Calcium intervention

The 276 participants who completed the vitamin D intervention study were randomised to treatment with calcium one tablet each day (n = 138), or placebo one tablet each day (n = 138). The treatment period of 14 days was completed by 269 participants. Of the seven drop-outs, three died, three became terminally ill and one participant dropped out for unknown reasons. Only those treated with vitamin D were included in the analysis of the calcium intervention (n = 68 for calcium; n = 71 for placebo); there was only one drop-out in each group.

Effectiveness of Vitamin D supplementation

Nursing home and potential confounding variables at baseline were not included in the final models since the effect sizes were hardly influenced by adding these variables.

Serum 25-hydroxyvitamin D

Effects of vitamin D supplementation on serum 25(OH)D in the various treatment groups are shown in Table 2 and Fig. 2. The mean difference in increase of serum 25(OH)D was 38.5 nmol/L (95% confidence interval (CI) 25.6–41.5) in favour of vitamin D when compared to placebo. Daily, weekly and monthly administration of vitamin D resulted in increase of serum 25(OH)D when compared to placebo ($P < 0.001$). The mean difference in increase of serum 25(OH)D was highest after 4 months with daily administration of vitamin D (mean 47.2 nmol/l) when compared to weekly (mean 40.7 nmol/l, $P < 0.01$) and monthly (mean 27.6 nmol/l, $P < 0.001$) administration. Weekly administration of vitamin D resulted in a greater increase of serum 25(OH)D than monthly administration ($P < 0.001$). The percentage of patients with serum 25(OH)D below cut offs of 25 nmol/l, 50 nmol/l and 75 nmol/l is shown in Table 3. At 4 months, the percentage of patients with serum 25(OH) D < 50 nmol/l was 10.9, 10.6 and 36.4% in the daily, weekly and monthly groups of vitamin D supplementation respectively.

table 2. Mean and standard deviation (SD) or median and interquartile range (IQR) for biochemical measurements at baseline (t_0), after 2 months (t_1) and after 4 months intervention (t_2) with placebo (Pl) or vitamin D (D) daily, weekly, or monthly in 276 participants.

		Mean (SD) or median (IQR)			Groups[a]	Mean difference[b] or ratio geometric means[c] (95% CI)	*P* value[b]	Groups[a]	Mean difference[b] or ratio geometric means[c] (95% CI)	*P* value[b]
Serum concentration		t_0	t_1	t_2		$t_0 \rightarrow t_2$	$t_0 \rightarrow t_2$		$t_0 \rightarrow t_2$	$t_0 \rightarrow t_2$
25(OH)D (nmol/L)	Pl	25.2 (12.1)	24.3 (11.2)	25.5 (12.0)	D/Pl	38.5 (35.7-41.3)	0.000			
	D daily	23.0 (8.3)	59.9 (16.5)	69.9 (17.8)	Dd/Pld	47.2 (42.3-52.1)	0.000	Dd/Dw	6.6 (1.7-11.4)	0.009
	D weekly	27.3 (12.7)	58.8 (12.8)	67.2 (14.0)	Dw/Plw	40.7 (35.8-45.6)	0.000	Dw/Dm	11.2 (6.3-16.1)	0.000
	D monthly	23.8 (8.0)	44.8 (14.1)	53.1 (15.9)	Dm/Plm	27.6 (22.8-32.5)	0.000	Dm/Dd	-17.8 (-22.7 - -12.8)	0.000
Phosphate (mmol/L)	Pl	1.04 (0.12)	1.05 (0.14)	1.01 (0.14)	D/Pl	0.057 (0.025-0.088)	0.001			
	D daily	1.01 (0.14)	1.07 (0.12)	1.05 (0.11)	Dd/Pld	0.088 (0.033-0.143)	0.002	Dd/Dw	0.022 (-0.033-0.076)	0.434
	D weekly	1.03 (0.15)	1.06 (0.13)	1.04 (0.14)	Dw/Plw	0.065 (0.01-0.12)	0.022	Dw/Dm	-0.001 (-0.055-0.054)	0.981
	D monthly	1.02 (0.13)	1.07 (0.16)	1.04 (0.12)	Dm/Plm	0.017 (-0.037-0.072)	0.533	Dm/Dd	-0.021 (-0.076-0.034)	0.454
Calcium corrected (mmol/L)	Pl	2.42 (0.10)	2.40 (0.09)	2.42 (0.09)	D/Pl	0.029 (0.008-0.05)	0.007			
	D daily	2.42 (0.10)	2.42 (0.10)	2.45 (0.10)	Dd/Pld	0.036 (0-0.071)	0.050	Dd/Dw	0.006 (-0.03-0.042)	0.736
	D weekly	2.41 (0.08)	2.41 (0.10)	2.43 (0.10)	Dw/Plw	0.019 (-0.018-0.055)	0.307	Dw/Dm	-0.001 (-0.036 - 0.035)	0.974
	D monthly	2.42 (0.09)	2.42 (0.09)	2.44 (0.10)	Dm/Plm	0.033 (-0.003-0.068)	0.072	Dm/Dd	-0.005 (-0.041-0.03)	0.762
PTH (pmol/L)[c]	Pl	7.2 (5.0-11.8)	7.8 (5.6-10.8)	7.5 (5.1-11.0)	D/Pl	0.77 (0.7-0.85)	0.000			
	D daily	7.3 (5.0-10.3)	5.7 (4.3-7.4	5.1 (3.7-7.7)	Dd/Pld	0.66 (0.56-0.78)	0.000	Dd/Dw	0.83 (0.7-0.99)	0.037
	D weekly	6.5 (5.3-9.5)	6.5 (4.6-8.7)	5.9 (5.2-7.6)	Dw/Plw	0.85 (0.72-1.01)	0.067	Dw/Dm	1.02 (0.86-1.22)	0.773
	D monthly	7.2 (5.1-10.9)	6.6 (4.4-9.3)	5.6 (4.3-8.9)	Dm/Plm	0.81 (0.68-0.96)	0.019	Dm/Dd	1.17 (0.99-1.39)	0.061

		Mean (SD) or median (IQR)			Groups[a]	Mean difference[b] or ratio geometric means[c] (95% CI)	*P* value[b]	Groups[a]	Mean difference[b] or ratio geometric means[c] (95% CI)	*P* value[b]
CTX	Pl	598 (270)	612 (274)	624 (256)	D/Pl	-14 (-57-29)	0.491			
	D daily	578 (267)	574 (265)	579 (279)	Dd/Pld	-34 (-109-41)	0.341	Dd/Dw	1 (-73-75)	0.976
	D weekly	606 (316)	599 (314)	595 (304)	Dw/Plw	-27 (-102-48)	0.445	Dw/ Dm	-36 (-111-39)	0.314
	D monthly	490 (207)	528 (229)	523 (230)	Dm/Plm	19 (-56-93)	0.589	Dm/ Dd	35 (-40-110)	0.329
AF (U/L)[c]	Pl	84 (67-99)	82 (69-99)	82 (67-101)	D/Pl	0.97 (0.92-1.03)	0.363			
	D daily	82 (72-99)	88 (69-101)	82 (67-97)	Dd/Pld	0.96 (0.87 - 1.06)	0.412	Dd/Dw	0.96 (0.87-1.06)	0.394
	D weekly	88 (66-107)	81 (64-105)	80 (69-104)	Dw/Plw	1.03 (0.93 - 1.14)	0.553	Dw/ Dm	1.1 (1\-1.21)	0.057
	D monthly	86 (67-103)	80 (64-96)	74 (63-100)	Dm/Plm	0.94 (0.85-1.03)	0.180	Dm/ Dd	0.95 (0.86-1.05)	0.270

[a] Differences in mean change between following groups: D/Pl = vitamin D versus placebo; Dd/Pld = vitamin D daily versus placebo daily; Dw/Plw = vitamin D weekly versus placebo weekly; Dm/Plm = vitamin D monthly versus placebo monthly; Dd/Dw = vitamin D daily versus weekly; Dw/Dm = vitamin D weekly versus monthly; Dm/Dd = vitamin D monthly versus daily.

[b] Mean difference of for example 38.5 for 25(OH)D (D/Pl) means that the mean increase of 25(OH)D over 4 months was 38.5 in the vitamin D group compared to zero (set as a reference) in the placebo group.

[c] For PTH and AF the ratio of geometric means (resembling the ratio of medians) is presented instead of the mean difference. Ratio of geometric means of 0.77 for PTH (D/Pl) means that the median PTH decreases with a ratio of 0.77 over 4 months in the vitamin D group compared to a ratio of 1.00 (set as a reference) in the placebo group.

Secondary outcome measures: serum phosphate and corrected calcium

Serum phosphate and corrected serum calcium values increased significantly more in the vitamin D group than in the placebo group. However, no differences between daily, weekly, or monthly administration were found (Table 2).

Serum parathyroid hormone and bone turnover markers

Effects of vitamin D supplementation on serum PTH, serum APh and CTX in the various treatment groups are shown in Table 2. Serum PTH ($P < 0.000$) decreased in the vitamin D group from 7.2 to 5.5 pmol/l when compared to placebo, which is a decrease of 23% (ratio 0.77, 95% CI 0.70–0.85, < 0.001). The decrease of serum PTH was greater with daily administration of vitamin D when compared to weekly ($P < 0.05$) and monthly ($P < 0.10$) administration. The difference between weekly and monthly administration of vitamin D was not significant. The serum concentrations of alkaline phosphatase and CTX did not change following vitamin D supplementation.

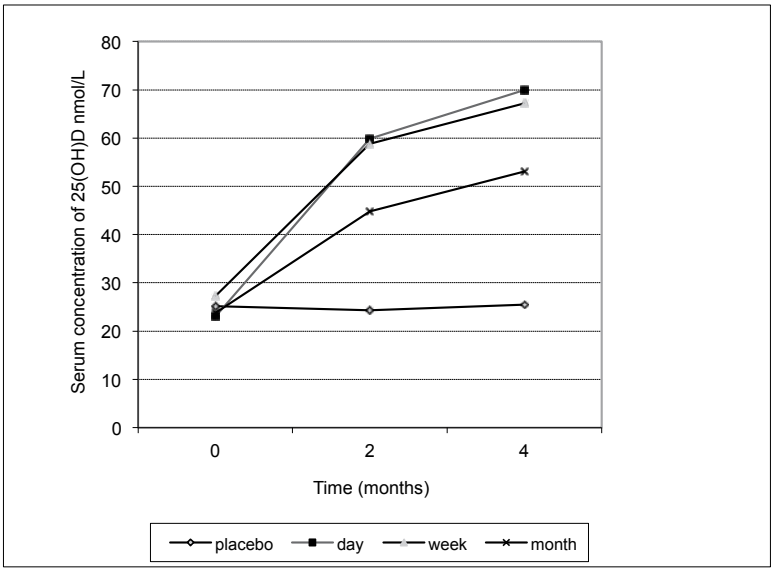

figure 2. Mean (± 1.96 × SD) serum 25(OH)D concentrations at baseline, 2 and 4 months during treatment with vitamin D daily, weekly, or monthly, or placebo

table 3: Percentage of participants with 25(OH)D levels below a certain cut-off point at baseline and after vitamin D or placebo supplementation.

Group	Total	Placebo	D total	D Daily	D weekly	D monthly
25(OH)D < 25 nmol/L						
Baseline (t0)	55.3	56.9	53.6	60.9	48.9	51.1
2 months (t1)	30.1	57.8	2.9	2.2	0.0	6.8
4 months (t2)	27.4	52.6	2.2	2.2	0.0	4.5
25(OH)D < 50 nmol/L						
Baseline (t0)	97.5	96.4	98.6	100.0	95.7	100.0
2 months (t1)	65.4	94.8	36.5	26.1	19.1	65.9
4 months (t2)	58.0	97.1	19.0	10.9	10.6	36.4
25(OH)D < 75 nmol/L						
Baseline (t0)	99.6	99.3	100.0	100.0	100.0	100.0
2 months (t1)	95.2	99.3	91.2	87.0	89.4	97.7
4 months (t2)	88.3	100.0	76.6	63.0	72.3	95.5

Effectiveness of calcium supplementation
There was no effect of calcium supplementation on any of the six biochemical outcome variables when compared to placebo. Also after stratification by administration of vitamin D (daily, weekly or monthly), an effect of calcium supplementation was not observed except for corrected calcium levels which increased more in the calcium group than in the placebo group in the daily dose vitamin D group only ($P < 0.05$). No effect was found of calcium doses (800 mg vs 1,600 mg calcium carbonate). Adding nursing home and other potential confounding variables at baseline did not influence the results.

Fractures
The number of falls and fractures did not differ between the intervention groups and the control groups, which was expected given the short study period of four and a half months.

Compliance
The compliance assessed within 96 random samples of the returned medication was good. In the daily administration group, all 33 participants were compliant–i.e., used at least 80% of the tablets–(median = 97.0; IQR 94.5–100). For weekly administration, 80% of the 35 participants were compliant–i.e., used at least 80% of the tablets (median = 98.5; IQR 84.0–100). For monthly administration, 93% of the 28 participants were compliant–i.e., used at least four out of five powders (median = 100; IQR 85.0–100).

Survey nursing staff
A survey among the nursing staffs of the participating nursing home wards showed a distinct preference (72%) for daily administration compared to weekly and monthly. Thirty nine percent of the nursing staffs reported the impression that fewer mistakes were made using daily administration instead of weekly or monthly administration.

Discussion

The results of this study confirm the poor vitamin D status often observed in institutionalised elderly. In this study, baseline serum 25(OH)D levels in these nursing home residents was comparable to those observed in other studies in institutionalised elderly in the Netherlands [2, 3], resulting in median serum PTH levels in the upper normal range. A negative correlation between serum PTH and serum 25(OH)D was observed, confirming other studies [4]. In all treatment groups oral vitamin D supplementation appeared to be effective, resulting in increasing serum 25(OH)D levels and decreasing serum PTH levels as observed in other studies [3, 4, 23]. However, no effect was seen on serum alkaline phosphatase and CTX levels. Daily administration of vitamin D3 was significantly more effective than weekly and monthly administration. This could be due to more regular absorption in the gut or better compliance. The percentage of participants with serum 25(OH)D < 50 nmol/l after four months of supplementation was about 10%

in the daily and weekly groups, but was more than 35% in the monthly group. An option would be to increase the dose when vitamin D is supplemented only once per month. The dose of 600 IU/day was chosen according to the Dutch and US recommendations [4, 18]. In order to attain a higher percentage of people with serum 25(OH)D > 50 nmol/l, the dose of vitamin D should be 700–800 IU/day as was recommended for patients with osteoporosis in a recent review [24]. The overall decrease of serum PTH was 23% with vitamin D supplementation, which corresponds to our previous vitamin D supplementation study in a nursing home [15] and which is a larger decrease than that observed in healthy independently living elderly women where the decrease of serum PTH was 15% [8]. This is consistent with the more severe vitamin D deficiency and the greater degree of secondary hyperparathyroidism observed in these, mainly psychogeriatric, nursing home residents. Improvement of vitamin D status and suppression of PTH secretion may reduce bone turnover and bone loss, increase bone mineralization and thereby reducing fracture risk, although this was not the subject of this study. For calcium supplementation, calcium citrate, lactate or carbonate can be used. In this study, calcium carbonate was used based upon bioavailability, cost and clinical efficacy [25]. The absorption of calcium from dairy products is about similar to that from calcium carbonate [26, 27]. Because of the side effects of calcium carbonate (gastrointestinal irritation, constipation, belches), possibly more pronounced in a population of frail elderly with substantial comorbidity and co-medication, one should not choose a too high supplementation dose. Given the expected dietary calcium intake of about 900 mg per day, two supplementation doses 800 mg calcium carbonate (320 mg Ca2+) and 1,600 mg calcium carbonate (640 mg Ca2+), respectively) were used.

The median calcium intake in these Dutch nursing home residents (750 mg per day from dairy products, total estimated dietary intake 950–1,000 mg per day) was slightly lower than the guidelines recommend and relatively high compared to institutionalised elderly in other countries, probably due to a higher dairy intake. This was expected since every Dutch nursing home has its own dietician. Calcium supplementation combined with vitamin D in the last part of the study did not lead to a decrease of biochemical markers of bone turnover. An explanation might be that immobility is a cause of high bone turnover, which is not suppressed by calcium supplementation.

The nursing staff's preference for daily supplementation of vitamin D is probably due to the fact that it fits better in a regular distribution routine, is less time consuming and less susceptible for making mistakes.

In conclusion, 98% of the participants had a baseline serum 25(OH)D lower than 50 nmol/L. Oral vitamin D3 supplementation, administered daily was more effective than weekly doses in nursing home residents, while monthly administration was the least effective, 35% still having a serum 25(OH)D < 50 nmol/l after 4 months treatment in this group. Calcium supplementation did not augment the effect of vitamin D supplementation.

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Chapter 5

Vitamine D suppletie bij ouderen: advies versus praktijk

Victor Chel, specialist ouderengeneeskunde,[1,2] dr. Petra Elders, huisarts,[3] Margot Tuijp, kaderhuisarts ouderengeneeskunde,[4] dr. Henk van den Berg, voedingskundige,[5] Karen van Drongelen, projectmanager Gezonde start,[5] Regine Siedenburg, apotheker,[6] dr. Marcel Ooms, arts-epidemioloog,[2] prof. dr. Paul Lips, internist – endocrinoloog[2,7]

(1) Verpleeg-, behandel- en huntingtoncentrum Topaz Overduin Katwijk
(2) EMGO- instituut, VU medisch centrum Amsterdam
(3) Afdeling huisartsgeneeskunde en ouderengeneeskunde VU medisch centrum Amsterdam
(4) te Utrecht
(5) Voedingscentrum [HvdB tot 31-12-2011]
(6) De Mensen Apotheek Sassenheim
(7) Sectie endocrinologie, afdeling Interne Geneeskunde VU medisch centrum Amsterdam

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Samenvatting

doel: In 2008 publiceerde de Gezondheidsraad een advies met betrekking tot vitamine D suppletie aan ouderen. Desondanks is bij het ministerie van VWS en het Voedingscentrum het vermoeden gerezen dat vitamine D suppletie bij ouderen nog onvoldoende plaatsvindt. Wij wilden nagaan in hoeverre specialisten ouderengeneeskunde het gezondheidsraad-advies ook daadwerkelijk opvolgen.
opzet: enquêteonderzoek
methode: Wij hebben alle specialisten ouderengeneeskunde in Nederland een korte enquête gestuurd en daarnaast ter vergelijking enige vragen voorgelegd aan huisartsen op een netwerkbijeenkomst van het Academisch Netwerk Huisartsgeneeskunde van het VUmc te Amsterdam.
resultaten: Ruim twee derde van de respondenten, zowel specialisten ouderengeneeskunde als huisartsen, is bekend met het suppletieadvies van de Gezondheidsraad, maar ongeveer de helft suppleert niet als dat wel zou moeten . Voor zover zij wel suppleren, geeft ongeveer de helft van de specialisten ouderengeneeskunde en een vijfde van de huisartsen een te lage dosis.
conclusie: Specialisten ouderengeneeskunde houden zich onvoldoende aan de adviezen van de Gezondheidsraad. Waarschijnlijk geldt dit ook voor huisartsen. De vitamine D-suppletieadviezen hebben nog te weinig draagvlak onder zorgverleners en zijn nog te weinig bekend.

Abstract

Vitamin D supplementation in the elderly: guidelines and practice
objective: In 2008, the Health Council of the Netherlands published an advice on vitamin D supplementation for the elderly. Nevertheless, suspicion arose at the Ministry of Health, Welfare and Sport and the Netherlands Nutrition Centre that vitamin D supplementation in the elderly is still insufficient. We aimed to determine the extent to which elderly care physicians actually followed the advice of the Health Council.
design: questionnaire study.
method: Brief questionnaires were sent to all elderly care physicians in the Netherlands. For comparison some questions were also posed to general practitioners at a network meeting of the Academic Network of GP Practices of the VU University Medical Center in Amsterdam.
results: More than two-thirds of the respondents, both elderly care physicians and general practitioners, are familiar with the guidelines of the Health Council of the Netherlands on vitamin D supplementation in the elderly, but about half do not prescribe vitamin D when the guideline advises to do so. When supplementation is prescribed, about half of the elderly care physicians and a fifth of the general practitioners uses an insufficient dose.
conclusion: The guidelines of the Health Council of the Netherlands on vitamin D supplementation in the elderly are not sufficiently followed by elderly care physicians and probably also not by general practitioners. Awareness of and support for the vitamin D supplementation guidelines among health care providers is still limited.

Inleiding

Dat vitamine D een belangrijke rol speelt bij de mineralisatie van botweefsel en bij de spierfunctie is bekend,[1-3] maar de gezondheidseffecten zijn mogelijk breder. De laatste tijd is er steeds meer aandacht voor de fysiologische rol van vitamine D bij auto-immuunziekten, coloncarcinoom en hart- en vaatziekten; ook het effect op de kwaliteit van leven wordt onderzocht.

In dit tijdschrift verscheen enige tijd geleden een overzicht van ziektebeelden die geassocieerd zijn met vitamine D-gebrek, waarin de recente inzichten over suppletie aan de orde kwamen[4]. Vitamine D-gebrek komt veel voor bij mensen op oudere leeftijd, in het bijzonder bij geïnstitutionaliseerde ouderen [1-6]. Suppletie van vitamine D, al of niet in combinatie met calcium, kan bij ouderen het aantal valpartijen, heupfracturen en andere perifere fracturen met 10-20% terugdringen [7-12].

Voornamelijk op basis van de relatie tussen vitamine D-gebrek, osteoporose en val- en fractuurrisico heeft de Gezondheidsraad in september 2008 haar standpunt over vitamine D suppletie voor ouderen aangepast. Het advies luidde sindsdien om dagelijks 20 µg (800 IE) cholecalciferol (vitamine D_3) te suppleren aan bewoners van verzorgings- en verpleeghuizen en aan ouderen die osteoporose of een donkere huid hebben, of weinig tot niet buiten in de zon komen [1]. Inmiddels is het advies opnieuw bijgesteld: sinds september 2012 adviseert de Gezondheidsraad 20 µg vitamine D per dag aan alle ouderen boven de 70 jaar, wat een vereenvoudiging en verduidelijking betekent ten opzichte van het advies uit 2008 [2].

In medicatiereviews bij ouderen, onder andere in verzorgingshuizen, vonden wij echter keer op keer dat deze adviezen niet breed nageleefd worden. Het is opvallend dat enerzijds experts discussiëren over de vraag of de dagdoseringen vitamine D niet veel hoger zouden moeten, terwijl anderzijds in de praktijk veel ouderen helemaal geen vitamine D suppletie krijgen. Onder andere naar aanleiding van zorgen over achterblijvende vitamine D suppletie heeft het Voedingscentrum in 2010, op verzoek van het ministerie van VWS, het initiatief genomen tot overleg met diverse koepelorganisaties en beroepsgroepen, met als een van de doelen verbetering van de suppletiegraad onder 70-plussers [13]. Tot op heden zijn echter nog geen gegevens verzameld over de mate waarin de betrokkenen – in het bijzonder specialisten ouderengeneeskunde en huisartsen – de adviezen van de Gezondheidsraad ook daadwerkelijk opvolgen.

Methode

Wij hebben in 2010 alle 1300 specialisten ouderengeneeskunde in Nederland een vragenlijst gestuurd, bestaande uit een A4'tje met 9 vragen. Het invullen kostte 1-2 minuten.

Omdat we de gegeven antwoorden wilden kunnen vergelijken met die van huisartsen, hebben we in 2011 een vragenlijstje van gelijke strekking voorgelegd aan de 42 huisartsen die aanwezig waren op de halfjaarlijkse netwerkbijeenkomst van het Academisch Netwerk Huisartsgeneeskunde (ANH) van het VUmc Amsterdam Het ANH bestaat uit 51 huisartsen

in de omgeving van Amsterdam. Beide vragenlijsten staan als supplement bij dit artikel op www.ntvg.nl/A5779 en aan het einde van dit artikel.
In dit artikel bespreken we de uitkomsten van onze 2 korte enquêtes, en vergelijken die met de bevindingen uit de eerder genoemde consultatie van koepelorganisaties en beroepsgroepen.

Resultaten

Vitamine D suppletie door specialisten ouderengeneeskunde

Van de 1300 specialisten ouderengeneeskunde retourneerden er 648 (50%) het enquêteformulier. Van de 648 respondenten was 65% bekend met het suppletieadvies van de Gezondheidsraad (tabel) en vond 75% het persoonlijk zinvol om standaard vitamine D suppletie te geven. Toch gaf slechts 50% aan dat zij dit in de praktijk ook daadwerkelijk deden. Ongeveer de helft van de respondenten gaf aan dat er in hun verpleeghuis geen beleid bestond met betrekking met betrekking tot routinematige vitamine D-suppletie. Een iets groter deel van de respondenten (47%) meldde dat zij meestal dagelijks 400 IE vitamine D gaven, een iets kleiner deel (45%) gaf dagelijks 800 IE. Dat zou betekenen dat ruwweg slechts een kwart van de Nederlandse verpleeghuisbewoners op dit moment de aanbevolen dagdosis van 800 IE cholecalciferol krijgt. 6% van de respondenten gaf aan op indicatie de serumconcentratie van 25(OH)D te bepalen.

tabel: Resultaten van een enquête in 2010 onder 1300 specialisten ouderengeneeskunde met betrekking tot vitamine D suppletie bij ouderen. In de tabel staan de gegevens van de 648 (50%) specialisten ouderengeneeskunde die de enquête invulden en terugstuurden.

resultaten	n	%
totaal aantal respondenten	648	100
is bekend met advies Gezondheidsraad	419	65
verpleeghuis heeft beleid m.b.t. routinematige suppletie	344	53
vindt suppletie zinvol	487	75
suppleert actief	323	50
suppleert 20 µg (800 IE) per dag	294	45
suppleert 10 µg (400 IE) per dag	303	47
suppleert alleen vitamine D	307	47
suppleert vitamine D plus calcium	300	46
bepaalt serum-25(OH)D op indicatie	38	6

Vitamine D suppletie door huisartsen

De antwoorden van de 42 ondervraagde academische huisartsen (respons 100%) kwamen in grote lijnen overeen met die van de specialisten ouderengeneeskunde. Ruim twee derde was bekend met de suppletieadviezen van de Gezondheidsraad, maar 50% vergat altijd of bijna altijd vitamine D voor te schrijven aan mensen boven de 70 jaar,

en bij verzorgingshuisbewoners vergat zelfs 60% het. Van degenen die wel vitamine D voorschreven aan verzorgingshuisbewoners, deed 20% dat in een lagere dan de door de Gezondheidsraad geadviseerde dosis van 800 IE.

Beschouwing

Onze enquêtes maken aannemelijk dat een groot deel van de Nederlandse kwetsbare ouderen niet de aanbevolen vitamine D suppletie krijgt. In verpleeghuizen bleken ongeveer 75% van de specialisten ouderengeneeskunde op dit gebied te onderbehandelen en mogelijk geldt eenzelfde percentage ook voor verzorgingshuizen waar huisartsen de hoofdbehandelaar zijn. Bij deze laatste groep is voorzichtigheid geboden bij het interpreteren en generaliseren van de resultaten omdat de groep ondervraagde huisartsen heel klein was. De uitkomsten van de enquête onder alle specialisten ouderengeneeskunde lijken daarentegen met een respons van 50% representatief.
Volgens de 'Voedselconsumptiepeiling 1997-1998' gebruikte destijds nog niet 1% van alle 65-plussers een vitamine D-supplement en 7% een multivitaminepreparaat (deze preparaten bevatten meestal 5, soms 10 µg cholecalciferol) [14]. Volgens de 'Voedselconsumptiepeiling 2007-2010' gebruikte 25% van de 51- 69-jarigen een multivitaminepreparaat en 5% een vitamine D-supplement – deze peiling bevat geen gegevens over 70-plussers [15].
In verpleeghuizen is vitamine D-gebrek al langer een bekend probleem. Aan het eind van de jaren 80, toen men voor de serumconcentratie 25(OH)D een grenswaarde van 30 nmol/l aanhield, was de prevalentie van vitamine D gebrek onder verpleeghuisbewoners 75% [16]. Bij de grenswaarde van 50 nmol/l die men tegenwoordig hanteert, zal de prevalentie dus eerder nog hoger zijn geworden. In Nederlandse psychogeriatrische verpleeghuizen ligt de gemiddelde serumconcentratie 25(OH)D rond de 25 nmol/l, en is deze bij vrijwel alle bewoners lager dan 50 nmol/l [6, 17, 18]. Dat de onderbehandeling van dit probleem toch aanhoudt, is verrassend, want het nut van vitamine D suppletie bij ouderen is onderhand toch wel duidelijk beschreven.
De antwoorden op onze vragenlijsten wijzen erop dat op dit moment slechts ongeveer 25% van de verpleeghuisbewoners voldoende vitamine D binnenkrijgt. Hoe klein de ondervraagde groep huisartsen ook was, het is toch veelbetekenend dat ook door huisartsen uit een academisch netwerk, van wie men zou verwachten dat zij de richtlijnen bovengemiddeld naleven, vitamine D suppletie onvoldoende plaatsvindt.
Jaarlijks breken ongeveer 1500 bewoners van verzorgings- en verpleeghuizen een heup; adequatere vitamine D suppletie zou het aantal heupfracturen en andere perifere fracturen in deze populatie mogelijk met een extra 7,5-15% kunnen doen afnemen, wat neerkomt op ongeveer 112-225 heupfracturen per jaar [7, 12, 19].
Wat weerhoudt artsen ervan om ruimer vitamine D voor te schrijven? Dit is in 2011 besproken in de door het Voedingscentrum georganiseerde consultatieronde met verschillende koepelorganisaties en beroepsgroepen [13], en het onderwerp is ook aan de orde gesteld binnen het Academisch Netwerk Huisartsgeneeskunde van het

VUmc. In beide bijeenkomsten werd vooral het ontbreken van een gevoel van urgentie en twijfels over het nut en de opbrengst van vitamine D suppletie genoemd. In het bijzonder huisartsen hebben daarbij de overtuiging dat primaire preventie voor grote bevolkingsgroepen niet thuishoort en niet haalbaar is in de huisartsenzorg. In de consultatieronde van het Voedingscentrum werden als andere factoren ook nog genoemd de complexiteit van de leeftijdgrenzen die de Gezondheidsraad hanteerde in haar advies van 2008, het grote aanbod van vitamine D-preparaten en het ontbreken van eenduidig, aansprekend voorlichtingsmateriaal voor consumenten dat aansluit op bestaande informatie over voeding en leefstijl.
De kosten werden niet genoemd als mogelijke reden om van vitamine D suppletie af te zien, wat begrijpelijk is bij een kostenniveau vanaf 3 cent per persoon per dag. Ongeveer 50% van de specialisten ouderengeneeskunde schrijft combinatiepreparaten met calcium voor. Deze preparaten zijn 13-25 x duurder en niet gewenst als de calciuminname via zuivel voldoende is.
Om tegemoet te komen aan de behoefte aan betere voorlichting heeft het Voedingscentrum onlangs het digitale platform 'Alles over vitamine D' gelanceerd (www.voedingscentrum.nl/vitamineD). Hier vinden professionals van verschillende disciplines achtergrondinformatie over vitamine D, hulpmiddelen voor voorlichting en materialen voor consumenten. Met dit platform, gevoegd bij de vereenvoudigde adviezen van de Gezondheidsraad, moet een hogere vitamine D-suppletiegraad onder ouderen te bereiken zijn.

Omdat dit artikel zich richt op de implementatie van de vitamine D suppletieadviezen van de Gezondheidsraad in het kader van preventie, valt behandeling van, aan vitamine D gebrek gerelateerde, klachten, en daarmee ook de discussie over oplaadschema's en de veiligheid daarvan, buiten het bestek van dit artikel [20, 21].

Conclusie

Specialisten ouderengeneeskunde blijken de adviezen van de Gezondheidsraad met betrekking tot vitamine D suppletie bij ouderen in de praktijk onvoldoende op te volgen. Waarschijnlijk geldt dit ook voor huisartsen. Slechts ongeveer 25% van de bewoners in verpleeghuizen en mogelijk ook in verzorgingshuizen krijgt adequate suppletie.
De bekendheid met, en het draagvlak voor, de suppletieadviezen is dan ook voor verbetering vatbaar. Wellicht kunnen de in september 2012 verschenen 'Evaluatie van de voedingsnormen voor vitamine D', waarin de Gezondheidsraad haar advies uit 2008 heeft vereenvoudigd, en het nieuwe digitale platform 'Alles over vitamine D' dat is opgezet door het Voedingscentrum, hier verandering in brengen.

Leerpunten

– De adviezen van de Gezondheidsraad met betrekking tot vitamine D suppletie bij ouderen worden in de praktijk onvoldoende opgevolgd door specialisten ouderengeneeskunde en waarschijnlijk ook door huisartsen.
– Slechts ongeveer 25% van de bewoners van verpleeghuizen en mogelijk ook van verzorgingshuizen krijgt adequate vitamine D-suppletie.
– Gehoor geven aan de adviezen van de Gezondheidsraad zou bij verpleeg- en verzorgingshuisbewoners jaarlijks mogelijk 112-225 extra heupfracturen en andere perifere fracturen kunnen voorkómen.

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bijlage 1.
vragenlijst verstuurd aan specialisten ouderengeneeskunde

1.- *bestaat er in het verpleeghuis waar u uw hoofdwerkzaamheden verricht, een beleid om in principe standaard bij alle verpleeghuisbewoners (uitzonderingen daargelaten) vitamine D te suppleren?*
0 ja **0** nee

2.- *De grootste groep waar ik in mijn werk zorg voor draag, bestaat uit mensen met de volgde grondslag:*
0 psychogeriatrie **0** somatiek **0** revalidatie **0** palliatieve zorg

3.- *Ik vind het persoonlijk zinnig om standaard vitamine D te suppleren bij, in principe, alle verpleeghuisbewoners (uitzonderingen daargelaten).*
0 helemaal mee oneens; **0** mee oneens; **0** geen mening; **0** mee eens; **0** helemaal mee eens

4.- *Ik suppleer vitamine D in principe standaard bij alle verpleeghuisbewoners (uitzonderingen daargelaten)*
0 ja **0** nee

5.- *Als ik vitamine D suppleer, doe ik dat meestal als volgt*:
0 met alleen vitamine D **0** met een combinatiepreparaat: vitamine D + calcium

6.- *Als ik vitamine D suppleer, doe ik dat meestal als volgt:*
0 dagelijks **0** wekelijks **0** maandelijks **0** half jaarlijks **0** jaarlijks

7.- *Als ik vitamine D suppleer, doe ik dat meestal in een dosering die overeenkomt met een cholecalciferol / vitamine D dagdosering van:*
0 400 IE(10mcg) **0** 800 IE(20mcg)

8.- *Ik vraag regelmatig vitamine D serumspiegelbepalingen aan*
0 ja **0** nee

9.- *Ik ben globaal bekend met de inhoud van de laatste vitamine D richtlijn van de Gezondheidsraad uit 2008*
0 ja **0** nee

bijlage 2.
vragenlijst voorgelegd aan huisartsen

1. Vitamine D is belangrijk voor het skelet. Kunt u enkele andere klinische verschijnselen of aandoeningen noemen waarbij de vitamine D spiegel een rol speelt.

2. Recentelijk zijn er een aantal associaties van vitamine D met andere aandoeningen gevonden. Kunt u daar enkele van noemen?

Kunt u hieronder aangeven wat u als richtlijn aanhoudt ten aanzien van vitamine D suppletie.

Suppletieadvies vitamine D

	niet	400IE (10µg)	800IE (20µg)	anders, nl: ……
3. Allochtone vrouwen 50 -70 jaar	o	o	o	o
4. Allochtone mannen 50 -70 jaar	o	o	o	o
5. Autochtone vrouwen 50 -70 jaar	o	o	o	o
6. Autochtone mannen 50 -70 jaar	o	o	o	o
7 Mannen en vrouwen ≥70 jaar	o	o	o	o
8. Bewoners verzorgingstehuis	o	o	o	o
9. Osteoporosepatiënten	o	o	o	o

Hieronder volgen een paar verschillende mogelijkheden van voorschrijfgedrag van huisartsen ten aanzien van vitamine D. Wilt u voor iedere bewering een kruisje in het vakje zetten dat het meest op u van toepassing is.

	altijd waar	vaak waar	soms waar	zelden waar	nooit waar
10. Ik schrijf vitamine D voor of adviseer het gebruik van vitamine D bij thuiswonende bejaarden die zelden buiten komen	o	o	o	o	o
11. Ik schrijf vitamine D voor of adviseer het gebruik van vitamine D bij allochtone vrouwen ≥50 jaar	o	o	o	o	o
12.Ik schrijf vitamine D voor of adviseer het gebruik van vitamine D bij bewoners van verzorgingstehuizen	o	o	o	o	o
13. Ik vergeet om aan vitamine D te denken als het eigenlijk wel zou moeten	o	o	o	o	o

chapter 6

High prevalence of vitamin D deficiency and insufficiency in patients with manifest Huntington's disease: an explorative study

Victor G.M. Chel, MD,[1,2] Marcel E. Ooms, MD PhD,[2] Jessie van der Bent,[1] Fleur Veldkamp,[1] Raymund A.C. Roos MD PhD,[3] Wilco P. Achterberg MD PhD,[1,4] Paul Lips MD PhD,[2,5]

(1). Huntingtoncentre Topaz, Overduin, Katwijk, The Netherlands
(2). EMGO-institute, VU University Medical Center, Amsterdam, The Netherlands
(3). Leiden University Medical Centre, department of Neurology, Leiden, The Netherlands
(4). Leiden University Medical Centre, department of Public Health and Primary Care, Leiden, The Netherlands
(5) VU University Medical Center, department of Internal Medicine / Endocrinology, Amsterdam, The Netherlands

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Abstract

Vitamin D deficiency and insufficiency are common in older institutionalised people and known to be associated with muscle weakness, impaired balance and increased fall risk. Falls and balance problems are common in people with Huntington's disease (HD)**.** Despite this, the prevalence of vitamin D deficiency in patients with manifest HD has never been investigated.

Serum 25(OH)D levels were measured in routinely drawn blood samples from 28 Dutch institutionalised patients with manifest Huntington's disease.

Mean serum 25(OH)D level was 33 nmol/l (SD 15). 25 subjects (89%) were vitamin D deficient or insufficient (25(OH)D < 50 nmol/L). A positive association was found between serum 25(OH)D levels and Functional Ambulation Classification (FAC) scores (p=0.023).

Introduction

Severe vitamin D deficiency (25(OH)D < 12.5 nmol/L), moderate vitamin D deficiency (12.5-25 nmol/l) and mild vitamin deficiency or vitamin D insufficiency (25-50 nmol/L) are common in older institutionalised people and known to be associated with muscle weakness, increased body sway, impaired balance and risk of falling [1-3]. Vitamin D deficiency is associated with type II muscle fibre atrophy. Type II muscle fibres are fast-twitch; the first to be recruited when trying to prevent a fall [4]. Increasingly, a causative or attributive role of vitamin D deficiency in multiple health problems is being discovered, such as the association with increased risk of common cancers, autoimmune diseases, insulin resistance and diabetes type 2, hypertension and neuropsychiatric disorders [2, 3, 5-9]. Despite advice from the Dutch Health Council of a daily supplementation of 800 IE (20 mcg) cholecalciferol to all nursing home residents in the Netherlands [10], vitamin D supplementation in institutionalised patients with Huntington's disease (HD) is not common. As far as we are aware there are no studies on the prevalence of vitamin D deficiency in patients with manifest HD.

Huntington's disease is a rare, inherited, progressive, neurodegenerative disorder of the central nervous system, characterized by motor impairments, psychiatric problems and dementia. It is autosomal-dominant inherited and caused by an elongated trinucleotide (CAG) repeat (36 repeats or more) on the short arm of chromosome 4p16.3 in the huntingtin gene [11]. The mean age at onset is between 30 and 50 years (range 2-85 years). Mean duration of HD is 17-20 years [11]. The pathophysiology of HD is not fully understood, although it is thought to be related to toxicity of the mutant huntingtin protein. The motor pattern is characterized by hyperkinesia (chorea, dystonia) and hypokinesia (bradykinesia), both leading to an increased risk of falls [11-13].

Falls and balance problems in patients with HD are common and multifactorial in origin 12, 13]. Falls, injury, impaired activities of daily living (ADL) with loss of independent ambulation eventually often leads to nursing home admission. Despite the potential harmful effects of vitamin D deficiency in patients with HD, little is known about the vitamin D status in this population. The aim of the study therefore was to explore the vitamin D status in our residential HD population, as a high degree of deficiency was suspected.

Patients and methods

Subjects were residents of Huntington Centre Topaz Overduin in The Netherlands with manifest, advanced HD. Physicians were asked to also determine serum 25(OH) D levels when they had the intention of drawing blood samples from their HD patients for any clinical indication. Therefore informed consent from subjects or there proxies was not obtained. Use of vitamin supplements was the only exclusion criterion. The best parameter for vitamin D status, 25-hydroxy-vitamin D (25(OH)D), was measured by a radioimmunoassay (25-OH-vitamin D RIA, Diasorin, Stillwater MN USA). The assay has 100% cross reactivity with 25(OH)D2 and 25(OH)D3. Total imprecision (Interassay coefficient of variation) is 9.4 % at 22 nmol/l. SCAL Medical Diagnostics (foundation central

primary care laboratory) is certified by RvA (Board of Accreditation) and participates in external quality assessment schemes organised by SKML (Foundation Quality Control Medical Laboratory Diagnostics).
In Huntington Centre Topaz Overduin, the standard of care contains regular assessments of Total Functional Capacity (Unified Huntington's Disease Rating Scale; UHDRS-TFC), Functional Ambulation Classification (FAC) and systematic administration of falls. Residents having had 2 falls or more over the past 12 months are called "recurrent fallers".
The UHDRS-TFC consists of five items that assess occupation, financial affairs, domestic chores, activities of daily living, and care level. Scores range from 0 to 13 (score 13 is normal; 0 is completely dependent [14].
The Functional Ambulation Classification consists of five items. Scores range from 0 to 5 (score 0 is Nonfunctional ambulation; 1: Ambulator-Dependent for Physical Assistance level II; 2: Ambulator-Dependent for Physical Assistance – level I; 3: Ambulator- Dependent for Supervision; 4: Ambulator- Independent Level Surfaces only; 5: Ambulator independent [15]. IBM SPSS statistics 20 was used to compute the descriptive parameters.
The association between vitamin D levels and FAC was determined by anova for ordinal scales.

Results

Over a period of approximately one year, blood samples were drawn from 28 subjects. Basic characteristics of the participants are listed in table 1.

table 1: basic characteristics of study population.

subjects (female / male) n	28 (15/13)
mean age (range) years	59 (42-76)
serum 25(OH)D, nmol/L mean (SD)	33 (15)
serum 25 (OH)-D in participants n(%) 25(OH)D < 75 nmol/L < 50 nmol/L < 25 nmol/L	 28 (100) 25 (89) 8 (29)
(UHDRS-)TFC score: 0 n(%) (UHDRS-)TFC score: 1 n(%)	25 (89) 3 (11)
FAC score: n(%) 0 1 2 3 4 5	 8 (29) 2 (7) 5 (18) 3 (11) 6 (21) 4 (14)
recurrent fallers (≥2x/year) n(%)	15(54)
subjects having sun exposure >1x/week n(%)	20 (71)
use of meal replacement products containing 25(OH)D, n(%)	 10 (36)

Routine care testing was the reason for blood sampling in 17 cases (61%). Other reasons were: fatigue (2 subjects); agitation (2 subjects); gastro-intestinal complaints (4 subjects); anemia (1 subject); weight loss (1 subject); change of behavior (1 subject). All participants but three had the lowest possible Total Functional Capacity (TFC). The mean age of the subjects was 59 (range 42-76). 20 subjects (71%), went outside in the sun at least once a week. Being an exclusion criterion, none of the subjects were using vitamin supplements, however, 10 subjects (36%) were using meal replacement products, mainly because of poor food intake. The extra daily vitamin D intake by using these products, calculated by a dietician, was between 88 IU (2.2 mcg) and 352 IU (8.8 mcg). One subject was bed ridden; 7 subjects (25%) were wheelchair bound; 7 subjects (25%) needed continuous help while walking and 13 subjects (46%) were able to walk without physical support, 15 subjects (54%) were considered to be "recurrent fallers".
Mean serum 25(OH)D level was 33 nmol/L (SD 15 range 6.5-58.2), 8 subjects (29%) were vitamin D deficient (25(OH)D < 25 nmol/L); 25 subjects (89%) vitamin D insufficient (25(OH)D < 50 nmol/L); 3 subjects (10%) were vitamin D sufficient (25(OH)D ≥ 50 nmol/L. No patient had a serum 25(OH)D level > 75 nmol/L.
A positive association was found between serum 25(OH)D levels and Functional Ambulation Classification (FAC) scores (p=0.023).

Discussion

This study is the first to demonstrate the high prevalence of vitamin D deficiency and insufficiency in institutionalised patients with manifest HD.
Huntington Centre Overduin houses 61 (long stay) patients with HD. Serum 25(OH)D levels were determined in a group of 28 subjects (46%). As the subjects were included only when blood sampling was necessary for any clinical indication, some bias may be present. The participants included in this study however did not differ substantially from the other institutionalised patients with manifest HD [16]. Another limitation is the size of this study although it was performed in one of the world's largest Huntington centers. Whether this study is generalizable to other countries is uncertain. While mass spectrometry is the current gold standard for measuring 25(OH)D, the used radioimmunoassay in this study is accurate and not influenced by vitamin D binding protein concentration [17].
The common vitamin D deficiency in older nursing home residents is mainly explained by the facts that older persons do not often go outside in the sunshine, the production of vitamin D in the skin decreases considerably with aging and dietary vitamin D intake is low. In an earlier study including 338 older nursing home residents with a mean age of 84 (± 6) years, mean serum 25(OH)D was 25.0 nmol/L (SD 10.9) at baseline, and in 98%, it was lower than 50 nmol/L. In that study participants did not go outside more than once a week. The total dietary vitamin D intake was estimated at about 100 IU/day and the calcium intake at 1000 mg/day [18]. Nursing home residents with HD are much younger than the average nursing home population and they come outside more often.
Most subjects (71%), went outside in the sun at least once a week and the FAC

demonstrates that this population was certainly not completely dependent. In addition 10 subjects (36%) used meal replacement products containing extra vitamin D3. However the mean serum 25(OH)D in institutionalised patients with manifest HD (33 nmol/L, SD 15, range 6.5-58.2) in this study was much lower than observed in another study (64.5 nmol/L, SD 39.3 range 19.5-99.5) in patients with pre-manifest HD [19]. Vitamin D deficiency is known to be associated with fracture risk and risk of falling. Although fracture is not a high risk in HD, recurrent falls are: in another Dutch study, in 45 early to mid-stage HD patients, no less than 60% of the participants reported two or more falls in the previous year [12]. In the present study, 15 subjects (54%) were considered to be "recurrent fallers". General policy in Dutch long stay facilities for people with HD is to preserve the autonomy of these patients as much as possible in order to maximize the quality of life. One of the consequences of this policy is that physical restraints are not used in any form, thereby accepting the fact that HD-patients fall frequently. A multidisciplinary team of physicians, physiotherapists, dietitians, occupational therapists, psychologists and nurses is employed with the aim of minimising the number and consequences of falls by periodic evaluation and, if possible, treatment of known multifactorial causes.

It is not known yet whether vitamin D deficiency is also associated with fall risk in HD. Given the high prevalence of vitamin D deficiency in nursing home residents with HD, it would be valuable to further investigate such a possible association, since vitamin D deficiency in nursing home residents is easy to treat with oral supplementation or ultraviolet irradiation [18, 20].

Furthermore, it would also be useful to examine a possible association of vitamin D deficiency in patients with manifest HD, and neuropsychiatric problems as often seen in HD. Such an association has not been investigated, but could well exist since vitamin D is known to have neurotrophic, neuroprotective and neurotransmissive properties. Moreover, vitamin D deficiency is associated with several neuropsychiatric disorders including schizophrenia, psychosis, depression, anxiety, irritability, behavior disorders and cognitive impairment [5]. The same neuropsychiatric symptoms are frequently seen in HD and known to have a profound impact on the perceived quality of life [11, 21].

Conclusion

The prevalence of vitamin D deficiency and insufficiency is high in institutionalised patients with manifest Huntington's disease. As it yet unknown whether in HD vitamin D deficiency is associated with fall risk and neuropsychiatric problems, further study is needed.

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Addendum

Since this is merely an explorative prevalence study, a control group was not deemed necessary. The study was done as a possible prelude to further research on vitamin D and Huntington's disease.

When interpreting results of vitamin D studies it is important however, to know what laboratory methods are used since a large inter-laboratory variation exists. The used radioimmunoassay by SCAL Medical Diagnostics (foundation central primary care laboratory) in this study is known to be accurate and not influenced by vitamin D binding protein concentration [17]. It would be interesting though to have a comparison with vitamin D measurements done in the same period by the same laboratory in people aged 75 and older, since a high degree of vitamin D insufficiency and deficiency is known to exist in this age group. After performing our prevalence study we were given access to the results of all the serum 25(OH)D measurements performed by SCAL Medical Diagnostics (adherence area: 500.000 people) in people aged 75 and older (institutionalised as well as living independently) over the same year we performed our study (2012): serum 25(OH)D level was measured 1836 times (indications not known). Mean serum 25(OH)D level was 48.3 nmol/L (SD 27.7) (SCAL reference value: < 50 nmol/l = insufficiency). Serum 25 (OH) level was < 75nmol/l in 1512 subjects (82.4%); < 50 nmol/l in 1112 subjects (60.6%) and < 25 nmol/l in 404 subjects (22%).

Chapter 7

General discussion

This thesis focuses on comparing different therapies to treat vitamin D deficiency in nursing home residents. In this chapter some methodological issues and main conclusions of this thesis will be discussed. Subsequently, implications for clinical practice and recommendations for future research will be considered.

7.1 Main findings and methodological issues

7.1.1 Effect of ultraviolet irradiation compared to oral vitamin D (Chapter 1)

Forty-five participants were randomised to receive either ultraviolet B (UV-B) irradiation (at half MED (Minimal Erythema Dose) on 1000 cm^2 of the lower back, three times a week during twelve weeks), oral vitamin D supplementation 400 IU/day, or no treatment. At that time, in 1992, the Dutch Nutrition Council considered a daily intake of 100-200 IU to be adequate for older people [1]. Although, according to the current views, a relatively low oral supplementation dose was used to compare the effects with those of UV-B, it is important to note that, after 12 weeks, mean serum 25(OH)D vitamin D was around 60 nmol/L in both groups, indicating that sufficient vitamin D levels were reached in most participants of both treatment groups. In both groups, the decrease of serum PTH was more than 30%. This study showed the use of (artificial) UV irradiation in routine treatment of vitamin D deficiency in nursing home residents to be equally effective as oral vitamin D in reaching an adequate improvement of the vitamin D status in this population. Although the ability to produce vitamin D is lower in the aged skin than at younger ages, the outcomes of this study showed that even the very aged skin is still capable of producing adequate amounts of vitamin D, during ultraviolet irradiation (UV). This is of importance since these findings not only show the feasibility of the use of (artificial) UV irradiation to treat vitamin D deficiency in nursing home residents; the results also underline the importance of nursing home residents coming outside into the sun more often.

7.1.2 The application of UV-B by using sunbeds in daily practice (Chapter 3)

In order to investigate the feasibility and effectiveness of weekly sunbed use (half body, full frontal UV irradiation at half MED, during eight weeks) in obtaining vitamin D sufficiency in 8 nursing home residents, a practice-based approached was chosen. The ease of use is an important condition in utilising UV irradiation on a large-scale as a possible vitamin D supplementation method in nursing homes. Therefore in this study easy-to-use sunbeds were used, with a safe, fixed irradiation dose: 50% of the MED for skin type 2, once a week, 2 minutes at 1 meter distance. It was shown that such UV irradiation by standardised sunbed use led to a significant increase in 25(OH)D levels in vitamin D deficient nursing home residents. A period of eight weeks with the irradiation frequency of once per week, however, was too short to reach sufficient serum levels of vitamin D in this population.

In this small pilot study it was calculated that in this population a participation of 8 subjects was sufficient to detect a relevant difference in serum 25(OH)D levels. It could be debated whether in this study a control group should have been included. However, since

in Dutch (psychogeriatric) nursing home residents a seasonal variation in serum 25(OH)D levels is not observed, as we showed in our earlier studies (Ch. 2,4), the inclusion of some extra, frail nursing home residents as a control group was considered not to be strictly necessary. In addition, the Health Council of the Netherlands advises to all nursing home residents to take a vitamin D supplement of 800 IU per day. This makes a placebo control group very difficult from an ethical point of view.

7.1.3 Efficacy of different oral vitamin D supplementation regimens (Chapter 4)
In this part of investigation the effect of equivalent oral doses of cholecalciferol 600 IU/day, 4200 IE/week and 18,000 IU/month on the vitamin D status was compared. A daily dose of 600 IU vitamin D was used in accordance with the Dutch Health Council guidelines at that time, in 2000 [2]. In this study 338 nursing home residents participated. The treatment period of four months was completed by 276 participants (82%). There were 62 (18%) drop outs of which 41 participants (12%) died during the study and 9 (3%) became terminally ill. This shows the importance of taking into account the relatively high mortality in nursing home residents when performing even a short study in this population. Daily vitamin D supplementation was slightly but significantly more effective in raising serum levels of 25-hydroxyvitamin D (25(OH)D) than weekly supplementation. Monthly administration was the least effective. At 4 months, the percentage of patients with serum 25(OH)D < 50 nmol/L was 10.9, 10.6 and 36.4% in the daily, weekly and monthly groups of vitamin D supplementation respectively. A survey among the nursing staffs of the participating nursing homes showed a distinct preference (72%) for daily administration compared to weekly and monthly doses. A large proportion, i.e. 39%, of the nursing staffs reported the impression that fewer mistakes were made using daily administration. This finding is also in accordance with the recently revised guidelines of the Health Council of the Netherlands: the Committee advises all persons aged 70 and over to take a daily supplement [3].

7.1.4 Vitamin D supplementation in elderly care practice (Chapter 5)
Surveys were sent to all elderly care physicians in The Netherlands. The response was 50% which is adequate. Although in general, results of reviews that explore the question how often “you do something” may not always be reliable, in this survey the response was large and framework conditions were as optimal as possible for an objective response: the questionnaire was short, the questions were simple and unambiguous and a postage-free reply envelope was attached. The outcomes of this explorative survey surprisingly showed an overwhelming undertreatment regarding vitamin D supplementation in nursing home residents: though more than 2/3 of the elderly care physicians were familiar with the guidelines of the Health Council of the Netherlands concerning vitamin D supplementation in older people [3], about 50% of them did not prescribe vitamin D where the guideline advises to do so. The same is true for the general practitioners. Moreover, when vitamin D supplementation was prescribed, the dose was too low in 50%. These findings emphasise the importance of a higher awareness among health care professionals regarding the negative health consequences of vitamin D deficiency in this population.

7.1.5 Prevalence of vitamin D deficiency in Huntington's disease (Chapter 6)

Nursing homes in the Netherlands often have specialised wards for specific patient groups, e.g. those with young onset dementia, Korsakov's syndrome and Huntingtons's disease (HD). Regardless the situation, general guidelines for nursing home residents are not automatically applied to these specific subgroups. For instance, despite the advice from the Dutch Health Council, vitamin D supplementation in nursing home residents with HD is not common, probably because HD patients are younger than the average nursing home resident and the prevalence of vitamin D deficiency in this group is not known. Subjects in our study were 28 long-stay residents (46% of a total of 61) of the largest Huntington Centre in Europe. The mean age of the subjects was 59 years (range 42-76). The outcome of the study showed that vitamin D deficiency and insufficiency (serum 25(OH)D <25 nmol/L, 50 nmol/L respectively) is highly prevalent in HD nursing home residents (89%). Mean serum 25(OH)D level was 33 nmol/L (SD 15 range 6.5-58.2). As the subjects were included only when blood sampling was necessary for any clinical indication or routine care testing, we may have obtained however a slight underestimation of the vitamin D status. The participants included in this study however, did not differ substantially from the other institutionalised patients with manifest HD as is apparent from the data observed in a study on fall risk, carried out in almost the same period in the general population of Huntington patients in the same institute [4].

In our prevalence study a positive correlation was found between serum 25(OH)D levels and Functional Ambulation Classification (FAC) scores. This may be entirely coincidental. Alternatively, poor ambulation may lead to decreased sun exposure and poor vitamin D status, or low serum 25(OH)D may lead to decreased physical performance and mobility [5, 6]. The size of this study, however, did not allow adjustment for covariables. Since this is a cross-sectional association, no inference can be made concerning causality or the direction of the relationship.

Although in absolute terms, this is a small study, a number of 28 participating long stay HD residents is relatively substantial given the rarity of this disease. Still the size of this study did not enable us to stratify the results by relevant determinants, such as disease severity, gender and age. This would have increased the generalisability of the findings to institutionalised HD patients in other settings and countries.

7.2 implications for clinical practice

7.2.1 Treatment of Vitamin D deficiency by ultraviolet irradiation

Although oral vitamin D-supplementation was shown to be effective in obtaining adequate serum 25(OH)D levels in nursing home residents, cutaneous vitamin D production by UV irradiation may be a suitable alternative.

Advantages of oral supplementation are the costs and the ease of administration. Disadvantages are the extra medication (in a population where polypharmacy is often a major issue) and the risk of intoxication.

The sun exposure combined with obtaining a tan contributes to a feeling of looking good,

which is, according to the American philosopher Sandra Lee Bartky, especially in old age, associated with well-being [7]. UV irradiation may also contribute to well-being by its possible positive effect on mood and its association with relaxation and endorphin release [8-11]. Especially the visible short to medium wavelengths in (sun) light (blue/green/ yellow) seem to be essential for the therapeutic effect of light on "seasonal affective disorder" [12]. The first part of the visible spectrum is always present in the light of sunbeds. Other advantages of using UV irradiation are the natural way of this method, the absence of risk of intoxication and the possible additional health benefits: the beneficial role of UV-B in some auto-immune diseases (multiple sclerosis; insulin-dependent diabetes mellitus and rheumatoid arthritis) is linked to suppression of T helper cell type 1 mediated immune responses. Moreover, possibly through several other mechanisms apart from vitamin D effects, UV radiation may have a direct immunosuppressive effect. UV-B can possibly up regulate secretion of TNF-alpha, IL-10 and T regulatory cells, providing both local and systemic immunosuppression [13-17]. In several observational studies an inverse correlation was found between sunlight and mortality and incidence of colorectal, prostate, breast and ovary cancer and it was questioned whether vitamin D synthesis is the only mechanism by which sunlight exerts its possible preventive effect on these cancers [13, 17-21]. It has also been proposed that sunlight, independently of vitamin D, has beneficial effects on blood pressure, ischaemic heart disease and cerebrovascular disease: the skin contains stores of nitrogen oxides which can be reduced to nitric oxide (a potent vasodilator and key regulator of blood flow) by UV radiation and it has been hypothesised that the possible benefits of sunlight on cardiovascular health are mediated by mobilisation of skin stores of nitrogen oxides to the systemic circulation [22-24]. Recently Liu et al. showed in volunteers that 1 hour after heat lamp exposure with or without UVA, plasma nitrite levels rose (nitric oxide is rapidly oxidised to nitrite in the circulation) and blood pressure dropped significantly after UVA exposure, but not after heat-only exposure. Serum 25(OH)D levels remained unaffected in both sessions [25].

On the other hand excessive sun or artificial UV exposure is considered to be the major cause of skin cancer and the question is whether this risk outweighs the mentioned health benefits of sunlight. It is however important to realise that for the production of vitamin D no exorbitant sun or artificial UV exposure is necessary.

UV radiation (100-400nm) is subdivided into UVC (100-280nm), UV-B (280-315 nm) and UVA (315-400nm). UV radiation up to 290 nm is blocked by the stratospheric ozone and more than 95% of the remaining radiant UV energy lies in the UVA band. However, 80% of the effective harmful UV dose (causing sunburn or skin carcinomas) in midday summer sunlight is attributable to UV-B, the same UV wavelengths necessary for cutaneous vitamin D production, and only 10-20% to UVA [26, 27]. UV lamps used in most sun beds emit mainly UVA with only a small fraction of UV-B (<2%) [27] but recent studies and reviews clearly confirm that indoor tanning or sunbed use is associated with increased risk of melanoma and non-melanoma skin cancer (still, about 50% of the harmful UV dose from these sun beds is attributable to UV-B). A higher risk is associated with use in early life (<25-35 years) [8, 27-31] and among sunbed users, young women (20 - 35 years) are overrepresented [32].

For the mutagenic effect of UV radiation not only dose but also frequency of the UV irradiation is of importance. A study by De Winter et al. revealed that a single 1.2 MED (Minimal Erythema Dose) of solar-simulated radiation to the skin of young people caused DNA damage that was completely repaired after 3-4 days [33]. DNA repair in the skin of older people requires approximately 2-3 times more time [34, 35]. However, it is not known yet how much DNA damage is caused in the skin of older Dutch nursing home residents and how long repair of DNA damage will take in this population when half the UV dose causing skin redness (0.5 MED) is applied, since at this time, no studies are known on this subject.

A considerably different situation develops when people are frequently exposed to high doses of (artificial) UV radiation. The skin does not get enough time to repair the damage properly which can lead to various mutations and eventually to development of skin cancer.

The two main types of skin cancer are melanoma (10%), the most malignant skin cancer and non-melanoma skin cancer (90%) subdivided in: basal cell carcinoma (BCC) (75-80%); squamous cell carcinoma (SCC) (20%) and rare tumours of the sebaceous or sweat glands (2%) [36]. SCC usually has a faster growing rate and has the ability to metastasise, whereas BCC grows slowly and the formation of metastases is very rare. Both these so-called non-melanoma skin tumors are well curable when diagnosed early [36].

In the Netherlands about 4,346 new patients with melanoma (676 in persons 75 years or older) and 7054 with non-melanoma skin cancer -basal cell carcinoma not included- (3860 in persons 75 years or older) were registered in 2009 [36]. In 2010, in the Netherlands, 783 persons died from melanoma skin cancer (211 persons 75 years or older) and 94 persons from non-melanoma skin cancer (75 persons 75 years or older) [37]. The 5-year survival rate of melanoma is currently 80% for all stages together. When a melanoma is diagnosed in people aged 70 years or older, in about 50% of the cases, melanoma thickness according to Breslow is exceeding 1.5 mm. A melanoma thicker than 3 mm has a relative 5-year survival rate of 40% in men and 55% in women [36]. In all age groups, but especially in older age, melanoma survival rates are better in women, probably because in men melanoma is more often localised at the trunk were it is diagnosed in a later stage [36]. Since 1989 increased incidence rates of melanoma and mortality rates from melanoma are observed in the Netherlands [37]. Especially in older people (≥ 65 years) incidence rates increased most steeply. Possibly, older people could have accumulated high amounts of sun exposure and accompanying sunburns during their (adolescent) life time, due to unawareness of its harmful effects [38].

The role that UV irradiation plays in increasing the risk of skin cancer, is different for the three types of skin cancer: in SCC the cumulative amount of UV radiation determines the risk [26, 39], in BCC and melanoma skin cancer, intermittent, unaccustomed sun exposures (holiday exposure) and numbers of sunburns, predominantly in early life (childhood and adolescence), are associated with increased risk [17, 26, 39-45]. It is important to note however, that UV radiation is not always a risk factor in developing melanoma skin cancer: it is know from clinical experience that melanoma also can

develop in sites that are hardly exposed to sunlight and non-intermittent, occupational, sun exposure is even associated with a small reduction in melanoma risk, probably due to protective mechanisms in the skin which can be partly mediated by vitamin D [41, 45-47]. In reducing melanoma risk, avoidance of intermittent intense sun exposures causing sunburns in childhood is assumed to have a greater impact than sun avoidance during adulthood [44]. This could be explained by the fact that in childhood, melanocytes may be more vulnerable to the adverse effects of UV irradiation because the (slow) growth and division of skin melanocytes occurs predominantly in early life, whereas with increasing age the number of melanocytes is diminishing [48-50]. It seems therefore reasonable to conclude that in nursing homes, where (skins of) residents are frequently inspected during the daily care routine, the disadvantages of using moderate UV irradiation to prevent vitamin D deficiency do not prevail over the possible benefits.

7.2.2 Efficacy of different oral vitamin D supplementation regimens

Several vitamin D supplementation regimens exist. In our study oral regimens were compared. Daily vitamin D3 supplementation was slightly but significantly more effective in raising serum levels of 25-hydroxyvitamin D (25(OH)D) than the weekly supplementation. The administration only once a month was the least effective. It may very well be that the absorption of vitamin D is less effective when larger supplementation dosages are used. In another Dutch study, in non-western immigrants, oral 100,000 IU vitamin D3, once in 3 months also appeared to be less effective in raising serum levels of 25(OH)D when compared to 800 IU once a day [51]. Oral supplementation with 500,000 IU vitamin D3 once a year compared to placebo, in 2256 older Australian community-dwelling women, even increased risk of falls and fractures (probably because of too high serum 25(OH)D levels (>150nml/l) during the first three months) [52], whereas four monthly, oral supplementation with 100,000 IU vitamin D3 was shown to prevent (self-reported) fractures in British older men and women living in the community [53]. Also when given intramuscularly, larger supplementation dosages may be less effective: annual intramuscular supplementation with 300,000 IU vitamin D2 compared to placebo, in 9440 older British men and women, was not effective in preventing non-vertebral fractures: in the intervention group a significant excess risk of hip fracture was found [54].

Possibly a single annual dose may not provide adequate serum 25(OH)D concentrations over a whole year. Another possible disadvantage of using high dosages or highly concentrated solutions is the risk of intoxication when used incorrectly: vitamin D intoxication is rare but when reported, it occurs in people who accidentally continue a high loading dose.

A generally advised upper limit has been set at 4000 IU/day for adults [55].

Since vitamin D is possibly more effective and safer when administered more frequently in a not too high dosage, a daily or weekly dosage is preferable for routine vitamin D supplementation in institutionalised older people.

In our study where 600 IU/day or 4200 IU/week was used, after 4 months, about 10% of the participants did not reach vitamin D serum levels ≥ 50 nmol/l. It is to be expected

that this percentage will be lower when a daily supplementation dose of 800 IU is used as the Dutch Health Council now advises. However, little is known about the percentage of nursing home residents not reaching vitamin D sufficiency when using such a daily dose. Recent data from Veleva B. et al. out of our own nursing home population show that in 71 psychogeriatric nursing home residents using cholecalciferol capsules (5600 IU/week) or drops (50,000 IU/ml; 3 drops = 7500 IU/week), 3 participants out of the 52 using capsules (≥ 3 months) did not reached vitamin D sufficiency (5.8%). Two of them were known to refuse medication on a regular base and one of them had a history of a recurrent bladder carcinoma, lung carcinoma and radiotherapy, cardiac disease and chronic renal failure. Compliance in the group using capsules was 96.1%. Surprisingly, in the 19 participants using vitamin D drops, 16 participants (68.4%) did not reach vitamin D serum levels ≥ 50 nmol/l. Compliance in the group using drops was 100%. It was concluded that in the large majority of nursing home residents, vitamin D supplementation by using cholecalciferol capsules containing 5600 IU, once a week (equal to 800 IU daily) will lead to vitamin D sufficiency. When choosing a vitamin D preparation for routine supplementation in nursing home residents, it is important to realise that there may exist a major difference in efficacy, even when the supplements are containing the same amount of vitamin D [56].

7.2.3 Vitamin D supplementation in elderly care practice

In approximately 25% of the 165,000 residents in Dutch residential and nursing homes a sufficient vitamin D supplementation dose (800 IE = 20 mcg/day) is prescribed. That means that in this population approximately 75% is undertreated. When all institutionalised older people in the Netherlands would be treated in accordance with the guidelines of the Health Council of the Netherlands [3], quality of life (QOL) in this population may improve. That regards primarily the effects of vitamin D supplementation on bone mineral density, fractures, muscle strength and falls, which are, at this time, the only evidence-based health benefits: vitamin D supplementation combined with adequate calcium intake lowers the falls and fracture risk in institutionalised older people with 10-20% [3, 57-59]. In the Netherlands, 1500 residents of residential and nursing homes sustain a hip fracture each year [60]. Therefore, adequate vitamin D supplementation would prevent some extra 7,5-15% hip and other non-vertebral fractures, which is equivalent to about 112-225 hip fractures.

Mean direct medical costs of a hip fracture (hospital + after care) are estimated at 14,000 euro (for a person ≥ 55 years) [61]. Vitamin D supplementation (880 IE/day) is not expensive, starting at 11 euro per person, per year. Abolishing undertreatment in institutionalised older people seems to be cost-effective and may improve QOL in this population: the additional costs of vitamin D supplementation is approximately 1.4 million euros per year (based on costs of the cheapest supplements only; costs of care not included) while approximately 1.6-3.2 million euros (112-225 hip fractures) can be saved. Cost-effectiveness depends on cost-conscious prescribing, since costs of the various vitamin D supplements differ considerably (0.03 – 0.76 euro/day).

Apart from cost-effectiveness, also moral considerations should be taken into account.

Vitamin D deficiency in older people is known to be very prevalent and an easy to prevent, unnatural condition with evident negative health risks. Therefore, not treating vitamin D deficiency in care dependent nursing home residents, especially since the Health Council of the Netherlands clearly advises to do otherwise, could be considered as negligence. In order to achieve adequate vitamin D supplementation in nursing home residents, it is desirable that vitamin D supplementation becomes a basic element in care plans for all nursing home residents. Moreover, the Health Care Inspectorate of the Netherlands (IGZ) should consider vitamin D supplementation as an indicator and standard for responsible care in nursing homes.

7.2.4 Prevalence of vitamin D deficiency in Huntington's disease

Huntington's disease is a rare, inherited, progressive, neurodegenerative disorder of the central nervous system, characterised by motor impairments, psychiatric problems and dementia. In the Netherlands approximately 1500 people suffer from this disease [62]. In HD, falls, injuries, impaired activities of daily living (ADL) with loss of ambulation may eventually lead to nursing home admission, often at young age.

Our study is the first to demonstrate the high prevalence of vitamin D deficiency and insufficiency in institutionalised HD patients. Although in nursing home residents vitamin D deficiency is known to be associated with risk of falling, it is not known yet whether also in this subgroup of nursing home residents, vitamin D supplementation will have a beneficial effect on fall risk. This is of importance, since fracture is not a high risk in HD, but recurrent falls are. As mentioned before, the Health Council of the Netherlands already advises daily supplementation by 800 IE (20mcg) cholecalciferol to all nursing home residents. Since vitamin D deficiency is highly prevalent in institutionalised HD patients, all nursing home residents with HD (although much younger than the average nursing home population) should be advised to take 800 IU cholecalciferol daily.

7.3 Future research

7.3.1 Treatment of vitamin D deficiency by ultraviolet irradiation

Although most of the health benefits of UV irradiation probably occur through the vitamin D pathway, it is not clear yet whether this account for all effects. Especially, the possible added value on quality of life in nursing home residents when using UV irradiation to supply vitamin D would be worthwhile to further investigate in this population. A research protocol has already been designed.

7.3.2 Efficacy of different oral vitamin D supplementation regimens

Little is known about the added value of rapid correction of vitamin D deficiency by using cholecalciferol loading dosages. Although in general even with a daily dose of 400 IE, vitamin D sufficiency can be reached within three months, it could be worthwhile to investigate the health benefits of a loading dose regimen in nursing home residents since life expectancy in this population is generally estimated at 1.5-2 years.

7.3.3 Vitamin D supplementation in elderly care practice

Currently, guidelines of the Health Council of the Netherlands concerning vitamin D-supplementation in older people are not sufficiently followed in practice by elderly care physicians and general practitioners. It would be worthwhile to conduct a follow up survey in about five years. By then, the recently launched information platform on vitamin D by the Nutrition Centre (Voedingscentrum) [63] and the renewed advice of the Health Council regarding vitamin D supplementation [3] could have contributed to a higher awareness of, support for and adherence to the vitamin D supplementation guidelines among health care providers resulting in a better prevention of vitamin D deficiency in older people. Although the response of our survey by mail was adequate, an online survey tool may further improve the response rate. Moreover, in the follow-up survey it could be considered to approach all general practitioners, instead of a selected group.

7.3.4 Vitamin D deficiency in Huntington's disease

Vitamin D deficiency is known to be associated with fracture risk and risk of falling. Although fracture risk is relatively low in HD, fall risk is high. It is not known yet whether vitamin D deficiency is also associated with fall risk in HD. Given the high prevalence of vitamin D deficiency in nursing home residents with HD, it would be worthwhile to further investigate such a possible association and the subsequent effect of vitamin D supplementation. It would also be useful to examine a possible association of vitamin D deficiency in nursing home residents with HD and neuropsychiatric problems often seen in HD. Such an association seems possible, since vitamin D deficiency is known to be associated with several neuropsychiatric disorders including schizophrenia, psychosis, depression, anxiety, irritability, behavior disorders and cognitive impairment [64]. The same neuropsychiatric symptoms are frequently seen in HD and they are known to have a profound impact on the perceived quality of life [65, 66]. A research protocol has already been designed.

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Chapter 8

Summary, conclusions and recommendations

Vitamin D deficiency and insufficiency is common in older people, especially in nursing home residents. Vitamin D deficiency is defined as a serum 25-hydroxyvitamin D (25(OH)D) level lower than 25 nmol/l. Vitamin D insufficiency is defined as a serum 25(OH)D between 25 and 50 nmol/l. Persons with a serum 25(OH)D of 50 nmol/l or higher are considered vitamin D sufficient. Vitamin D-supplementation is likely to improve the Quality of Life (QOL) in this population. This thesis focuses on comparing different vitamin D treatment modalities in nursing home residents.

In ***Chapter 1*** an overview of the history and physiology of vitamin D is given. Also the vitamin D status in older people is discussed as well as the different possible ways to prevent and treat vitamin D deficiency in older people. Finally in this chapter nursing homes and nursing home care in The Netherlands are described as well as the fact that the emphasis in Dutch nursing home care is especially on improving the quality of life (QOL) as experienced by the residents.

Chapter 2 describes a randomised clinical trial in 45 female nursing home residents on the effect of ultraviolet irradiation, compared with oral vitamin D, on the vitamin D status and parathyroid hormone concentration. Participants in this study were randomised to receive either ultraviolet B (UV-B) irradiation (at half the minimal erythemal dose on 1000 cm2 of the lower back, three times a week during twelve weeks), or oral vitamin D 400 IU/day, or no treatment. Main outcome measures were change in fasting serum levels of vitamin D metabolites, at 0, 2, 4, 8, and 12 weeks, in the treatment groups, compared with the control group. PTH(1–84) was measured at 0 and 12 weeks. Baseline serum 25-hydroxyvitamin D (25(OH)D) was lower than 30 nmol/l in 95% of the participants. It increased to a median value of around 60 nmol/l after 12 weeks both in the UV-B and vitamin D groups, whereas there was no change in the control group. Serum 1,25-dihydroxyvitamin-D increased significantly in the UV-B group. Serum calcium increased significantly in both treatment groups. Serum PTH decreased more than 30% in both treatment groups ($p < 0.001$), whereas there was no significant change in the control group. It was concluded that irradiation with UV-B in older nursing home residents for a few minutes per day, 3x/week, leads to adequate improvement of the vitamin D status. It is as effective as oral vitamin D3 in increasing serum 25(OH)D and suppressing secondary hyperparathyroidism.

In ***Chapter 3*** the results are presented of a pilot study on the feasibility and effectiveness of weekly sunbed use (half body, full frontal UV irradiation at half the minimal erythemal dose, during eight weeks) in obtaining vitamin D sufficiency in 8 nursing home residents. Main outcome measures were change in fasting serum levels of 25(OH)D and PTH at 0, 2, 4 and 8 weeks. At baseline, mean serum 25(OH)D was 28.5 nmol/L. Mean serum 25(OH)D levels increased to 46.5 nmol/L. Median serum PTH levels decreased by 20% after 8 weeks of treatment. It was concluded that UV irradiation leads to a significant increase in 25(OH) D serum levels. A period of eight weeks with the irradiation frequency of once per week however was too short to reach vitamin D-sufficiency.

In ***Chapter 4*** the outcomes of a randomised controlled trial on the effect of different doses and time intervals of oral vitamin D supplementation in 338 nursing home residents, spread over ten nursing homes in the Netherlands, are presented and discussed. In this study the effect of equivalent oral doses of cholecalciferol 600 IU/day; 4200 IE/week and 18,000 IU/month on vitamin D status was compared. After 4 months, calcium was added during 2 weeks, 800 mg calcium carbonate (320 mg Ca^{2+})/day or 1600 mg calcium carbonate (640 mg Ca^{2+})/day or placebo. The treatment period of four months was completed by 276 participants (82%). The treatment period of four and a half months was completed by 269 participants (80%). At baseline, mean serum 25(OH)D was 25.0 nmol/L (SD 10.9). In 77% of the participants, baseline serum 25(OH)D was lower than 30 nmol/L, in 98% lower than 50 nmol/L. The median daily calcium intake with dairy products was 750 mg (interquartile range 560-1030). The mean serum 25(OH)D levels increased to 62.5 nmol/L (after daily vitamin D3 69.9nmol/L, weekly 67.2 nmol/L and monthly 53.1 nmol/L, $p<0.001$ between groups) and the median serum PTH levels decreased by 23% ($p<0.001$). At 4 months, the percentage of patients with serum 25(OH)D < 50 nmol/L was 10.9, 10.6 and 36.4% in the daily, weekly and monthly groups of vitamin D supplementation respectively. After 4 months in the vitamin D supplemented groups, there was no decrease of bone turnover markers (CTX and alkaline phosphatase). No additional effect was found of the subsequent calcium supplementation. It was concluded that daily vitamin D supplementation was slightly but significantly more effective in raising serum levels of 25-hydroxyvitamin D (25(OH)D) than weekly supplementation. Monthly administration was the least effective. Calcium supplementation had no effect on serum PTH and bone turnover. A survey among the nursing staffs of the participating nursing homes showed a distinct preference (72%) for daily administration compared to weekly and monthly. 39 % Of the nursing staffs reported the impression that fewer mistakes were made using daily administration.

In ***Chapter 5*** the results from a survey study, among elderly care physicians and general practitioners, to adherence to the guidelines of the Health Council of the Netherlands, concerning vitamin D supplementation in older people, are presented and discussed. Short surveys were sent to all 1300 elderly care physicians in the Netherlands. At a meeting of the Academic Network of GP practices of the VU University medical center in Amsterdam (51 GPs), a short questionnaire was given to the 42 general practitioners present. 50% Of the elderly care physicians returned the questionnaire. It was shown that, although more than 2/3 of the respondents are familiar with vitamin D supplementation in older people, approximately 50% of the elderly care physician and general practitioners do not prescribe vitamin D when the guideline advises to do so. If supplementation is prescribed, 50% of the elderly care physicians and 20% of the general practitioners uses an insufficient supplementation dose. In a meeting with different occupational groups, organised by the Netherlands Nutrition Centre, as well as in a meeting of the Academic Network of GP practices of the VU University medical center in Amsterdam, the following possible explanations for not supplementing vitamin D in older people were reported: lack

of sense of urgency; doubts about the health benefits; the conviction that implementation of primary prevention in large groups of the population is not appropriate and not feasible in GP practices; the complexity of the applied age limits in earlier guidelines, the large range of different vitamin D prescriptions and the lack of clear, appealing information material for consumers. It is concluded in this chapter that in the Netherlands elderly care physicians and probably also general practitioners do not sufficiently follow the advice of the Dutch Health Council regarding vitamin D supplementation in older people. Familiarity with, and support for the Health Council advice could be improved. It is likely that both the new Health Council report "Evaluation of the nutritional standards for vitamin D" published in September 2012 and the digital platform www.voedingscentrum.nl/vitamin D from the Netherlands Nutrition Centre, can contribute to this improvement.

In ***Chapter 6*** the high prevalence of vitamin D deficiency and insufficiency is described in a special sub group of (relatively young) nursing home residents: patients with Huntington's disease. Huntington's disease is a rare, inherited, progressive, neurodegenerative disorder of the central nervous system, characterized by motor impairments, psychiatric problems and dementia. The mean age at onset is between 30 and 50 years (range 2-85 years). Mean duration of HD is 17-20 years. Serum 25(OH)D levels were measured in routinely drawn blood samples from 28 out of 61 (long stay) Dutch nursing home residents with Huntington's disease (46%). The mean age of the subjects was 59 (range 42-76). Twenty subjects (71%) went outside in the sun at least once a week. Being an exclusion criterion, none of the subjects was using vitamin supplements, however, 10 subjects (36%) were using meal replacement products containing vitamin D, mainly because of poor food intake.
Mean serum 25(OH)D level was 33 nmol/l (SD 15). Eight subjects (29%) were vitamin D deficient (25(OH)D < 25 nmol/L). In 25 (89%) participants, serum 25(OH)D was lower than 50 nmol/L. Three subjects (10%) were vitamin D sufficient (25(OH)D > 50 nmol/L. A positive association was found between serum 25(OH)D levels and Functional Ambulation Classification (FAC) scores (p=0.023). The study presented in this chapter is the first to describe the high prevalence of vitamin D deficiency and insufficiency in institutionalised HD patients and its possible health consequences in this younger than average population of nursing home residents.

In the general discussion, ***chapter 7,*** methodological considerations and main findings of the studies included in this thesis are discussed as well as possible implications of the findings for clinical practice and future research.

Main conclusions are:

- Most nursing home residents are vitamin D deficient or insufficient
- Although the aged skin is known to have a decreased capacity to produce vitamin D, even the very aged skin is still capable of producing adequate amounts of vitamin D, following ultraviolet irradiation (UV-B).
- Vitamin D treatment in nursing home residents by ultraviolet irradiation (UV-B) is equally effective as oral vitamin D supplementation in increasing serum 25(OH)D and suppressing secondary hyperparathyroidism.
- Vitamin D treatment by using sunbeds (UV-B exposure) is feasible and easy to perform in daily nursing home care practice and therefore a realistic alternative (with possible adjusted health benefits) for oral vitamin D supplementation in this population.
- Several vitamin D supplementation regimens exist. Daily and weekly vitamin D-supplementation are more effective in reaching vitamin D sufficiency than monthly administrations
- Vitamin D supplementation in Dutch nursing homes is open to improvement: approximately 75% of the nursing home residents is undertreated.
- The prevalence of vitamin D deficiency and –insufficiency is high in a specific subgroup of, younger than average, nursing home residents: patients with Huntington's disease (HD). Vitamin D supplementation in this group is not common practice. It has to be further investigated whether also in this population vitamin D- deficiency is associated with increased fall risk and neuropsychiatric symptoms often seen in HD.

A follow up survey after for instance five years is suggested, in order to investigate whether
the recently launched information platform on vitamin D by the Netherlands Nutrition Centre (Voedingscentrum) and the renewed advice of the Health Council regarding vitamin D supplementation will have contributed to a higher awareness of, and support for the vitamin D supplementation guidelines among health care providers resulting in a better prevention of vitamin D deficiency in older people.

Moreover, further research is recommended on the topics of:

- the possible association of vitamin D deficiency in nursing home residents with HD and fall risk and neuropsychiatric problems often seen in HD (A research protocol has already been designed).
- the added value of rapid correction of vitamin D deficiency by using cholecalciferol loading dosages in nursing home residents.
- the assumed added value on quality of life in nursing home residents when using UV irradiation in vitamin D supplementation (a research protocol has already been designed)

Recommendations:

- Several vitamin D supplementation regimens exist. Since vitamin D probably is more effective and safer when administered more frequently in a not too high dosage, a daily or weekly dose is recommended for routine oral vitamin D supplementation in institutionalised older people
- Since vitamin D deficiency is also very prevalent in institutionalised HD patients, all nursing home residents with HD should be advised to take 800 IU cholecalciferol daily, irrespective of their age.
- In order to achieve adequate vitamin D supplementation in nursing home residents, it is desirable that vitamin D supplementation as a basic element in all care plans, is considered as an indicator and standard for responsible care in nursing homes by the Health Care Inspectorate of the Netherlands (IGZ).

Samenvatting, conclusies en aanbevelingen

De behandeling van vitamine D gebrek bij Nederlandse verpleeghuisbewoners
Vitamine D deficiëntie en insufficiëntie komen veel voor bij ouderen, in het bijzonder bij bewoners van verzorgings- en verpleeghuizen. Bij 25-hydroxyvitamine D (25(OH)D) serumspiegels onder de 25 nmol/L spreekt men van vitamine D deficiëntie, bij spiegels tussen de 25 en 50 nmol/L van vitamine D insufficiëntie. Mensen met een 25(OH)D serumspiegel van 50 nmol/L of hoger worden vitamine D sufficiënt beschouwd.
Het is aannemelijk dat adequate vitamine D suppletie de kwaliteit van leven van verpleeg- en verzorgingshuisbewoners kan verbeteren.
Dit proefschrift richt zich primair op het vergelijken van verschillende vitamine D suppletiemethoden in het verpleeghuis.

In ***hoofdstuk 1*** wordt een inleidend overzicht gegeven van de geschiedenis en fysiologie van vitamine D. Ook wordt hier de vitamine D status van ouderen besproken met daarbij verschillende manieren om vitamine D gebrek in deze populatie te voorkomen dan wel te behandelen. Tot slot wordt in dit hoofdstuk stilgestaan bij de zorg zoals die in Nederlandse verpleeghuizen geleverd wordt. Deze zorg is primair gericht op "kwaliteit van leven" vanuit het perspectief van de bewoner.

Hoofdstuk 2 beschrijft een gerandomiseerd klinisch onderzoek bij 45 psychogeriatrische verpleeghuisbewoners naar het effect van bestraling met ultraviolet B licht (UV-B), vergeleken met dat van vitamine D suppletie per os, op de vitamine D status (serum 25(OH)D) en serumspiegels van parathyreoidhormoon (PTH).
De deelnemers werden gerandomiseerd in 3 groepen:
1. behandeling met UV-B (3x/week op 1000 cm^2 van de onderrug, met de helft van de Minimale Erytheem Dosis (MED), gedurende 12 weken),
2. vitamine D (cholecalciferol) per os (dagelijks 400 IE) of
3. geen behandeling.

Uitkomstmaten waren de veranderingen in nuchtere serumspiegels van calcidiol (25(OH) D), en calcitriol (1,25 $(OH)_2D$), gemeten bij aanvang van de studie en na resp. 2, 4, 8 en 12 weken en PTH (1-84), gemeten bij aanvang van de studie en na 12 weken.
Bij aanvang van de studie had 95% van de deelnemers een serum vitamine D spiegel die lager was dan 30 nmol/l. Na 12 weken was, zowel in UV-B als in de vitamine D groep, de mediane waarde gestegen naar rond de 60 nmol/l. In de controle groep bleven de spiegels gelijk. In de UV-B-groep was er sprake van een significante stijging van de serum calcitriol spiegels. In beide behandelgroepen namen de serum PTH spiegels met meer dan 30% af ($p < 0.001$); in de controlegroep werd geen significant verschil waargenomen.
Geconcludeerd wordt dat korte UV-B-bestralingen de vitamine D status bij verpleeghuisbewoners net zo goed kunnen verbeteren en daarbij een secundaire hyperparathyreoidie net zo goed kunnen onderdrukken als orale vitamine D suppletie.

In ***Hoofdstuk 3*** worden de uitkomsten van een pilot-onderzoek naar de toepasbaarheid en effectiviteit van zonnebankbestralingen bij de behandeling en preventie van vitamine D gebrek in het verpleeghuis besproken. Acht Psychogeriatrische verpleeghuisbewoners werden eenmaal per week, zittende in een Carendo®douchestoel, bestraald met UV licht (0,5 MED) op de gehele voorzijde van het lichaam. Uitkomstmaten waren de nuchtere serumspiegels van 25(OH)D en PTH bij aanvang van de studie, vergeleken met die na 2, 4 en 8 weken. Bij aanvang van de studie was de gemiddelde serumconcentratie van 25(OH) D 28,5 nmol/L, na 8 weken was deze gestegen naar 46,5 nmol/l. De mediane serum PTH spiegel was na 8 weken met 20% afgenomen. Geconcludeerd wordt dat wekelijkse UV bestralingen bij verpleeghuisbewoners de serum 25(OH)D spiegels significant doet stijgen, maar dat een periode van 8 weken te kort of een bestralingsfrequentie van 1x/week te laag is om vitamine D sufficiëntie te bereiken in deze populatie.

Hoofdstuk 4 is gewijd aan de resultaten van een gerandomiseerd dubbelblind placebogecontroleerd onderzoek, bij 338 verpleeghuisbewoners verdeeld over 10 verpleeghuizen, naar het effect op de vitamine D status, van orale vitamine D suppletie met verschillende doseringen en tijdsintervallen. De deelnemers kregen gedurende 4 maanden, ofwel placebo, of 600 IE cholecalciferol/dag dan wel een equivalente dosis 1x/week (4200 IE) of 1x/maand (18000 IE). Na 4 weken werd gedurende 2 weken, dagelijks, calciumcarbonaat (800 mg = 320 mg Ca^{2+}, of 1600 mg = 640 mg Ca^{2+}) of placebo toegevoegd. 276 deelnemers (82%) maakten de onderzoeksperiode van 4 maanden af en 269 deelnemers (80%) die van 4,5 maanden. Bij aanvang van het onderzoek was de gemiddelde 25(OH)D serumspiegel 25,0 nmol/L (SD 10.9); bij 77% van de deelnemers was deze lager dan 30nmol/L, bij 98% lager dan 50 nmol/L. De mediane dagelijkse calcium inname via zuivelproducten was 750 mg. Na 4 maanden was de gemiddelde 25(OH)D serumspiegel gestegen naar 62,5 nmol/L (in de “dag”, “week” en “maand”-groep naar resp. 69,9, 67,2 en 53,1 nmol/L, $p<0.001$ tussen de verschillende groepen). Na 4 maanden was het percentage van de deelnemers dat geen vitamine D sufficiëntie bereikt had in de “dag”, “week” en “maand”-groep resp. 10, 9, 10,6 en 36,4%.
De mediane PTH-spiegels waren in de met vit D behandelde groepen afgenomen met 23% ($p<0.001$). Er was geen afname van de botombouwparameters C-terminaal telopeptide (CTX) en alkalische fosfatase (AF). Ook werd er geen additioneel effect gezien van de toegevoegde calciumsupplementen. Geconcludeerd wordt dat dagelijkse en wekelijkse vitamine D suppletie effectiever zijn in het verhogen van vitamine D spiegels dan maandelijkse suppletie. Dagelijkse suppletie was vrijwel even effectief als wekelijkse alhoewel net significant iets effectiever. Calciumsuppletie had geen effect op PTH spiegels en botombouwactiviteit. Een enquête onder het verplegend personeel liet een duidelijke voorkeur (72%) zien voor de dagelijkse suppletievorm. 39% van de respondenten gaf aan de indruk te hebben dat de kans op fouten kleiner was bij dagelijkse suppletie.

In ***Hoofdstuk 5*** wordt verslag gedaan van een enquêteonderzoek dat tot doel had om na te gaan in hoeverre specialisten ouderengeneeskunde het Gezondheidsraad-advies met betrekking tot vitamine D suppletie bij ouderen, daadwerkelijk opvolgen. Aan alle specialisten ouderengeneeskunde in Nederland werd daartoe een korte vragenlijst gestuurd. Huisartsen van het Academisch Netwerk Huisartsgeneeskunde van het VU medisch centrum (VUmc) te Amsterdam kregen, ter vergelijking, tijdens een netwerkbijeenkomst een korte vragenlijst voorgelegd. Ook wordt in dit hoofdstuk stilgestaan bij de vraag wat artsen er mogelijk van weerhoudt om vitamine D voor te schrijven. Uit de enquête kwam naar voren dat ruim twee derde van de respondenten, zowel specialisten ouderengeneeskunde als huisartsen, bekend bleken te zijn met het suppletieadvies van de Gezondheidsraad en dat desondanks ongeveer de helft niet suppleerde als dat wel zou moeten. Voor zover zij wel suppleerden, schreef ongeveer de helft van de specialisten ouderengeneeskunde en een vijfde van de huisartsen een te lage dosis voor (400 in plaats van 800 IE). Redenen om geen vitamine D voor te schrijven kwamen naar voren in bovengenoemde netwerkbijeenkomst alsmede tijdens een door het Voedingscentrum georganiseerde consultatieronde met verschillende koepelorganisaties en beroepsgroepen. In beide bijeenkomsten werd vooral het ontbreken van een gevoel van urgentie en twijfels over het nut en de opbrengst van vitamine D-suppletie genoemd. In het bijzonder huisartsen hebben daarbij de overtuiging dat primaire preventie voor grote bevolkingsgroepen niet thuishoort en niet haalbaar is in de huisartsenzorg. In de consultatieronde van het Voedingscentrum werden als andere factoren ook nog genoemd de complexiteit van de leeftijdgrenzen die de Gezondheidsraad hanteerde in haar advies van 2008, het grote aanbod van vitamine D preparaten en het ontbreken van eenduidig, aansprekend voorlichtingsmateriaal voor consumenten dat aansluit op bestaande informatie over voeding en leefstijl.
Geconcludeerd wordt in dit hoofdstuk dat specialisten ouderengeneeskunde en mogelijk ook huisartsen de adviezen van de Gezondheidsraad met betrekking tot vitamine D-suppletie bij ouderen in de praktijk onvoldoende opvolgen. Slechts ongeveer 25% van de bewoners in verpleeghuizen en waarschijnlijk ook in verzorgingshuizen krijgt adequate suppletie. De bekendheid met, en het draagvlak voor, de suppletieadviezen is dan ook voor verbetering vatbaar.

Hoofdstuk 6 werpt licht op de (nog niet eerder beschreven) prevalentie van vitamine D gebrek bij verpleeghuisbewoners met de ziekte van Huntington. De ziekte van Huntington is een zeldzame, erfelijke, progressieve, neurodegeneratieve ziekte die gepaard gaat met bewegingsstoornissen, vallen, neuropsychiatrische problemen en dementie. De gemiddelde aanvangsleeftijd van deze ziekte is 30 tot 50 (2-85) jaar. De gemiddelde ziekteduur bedraagt 17-20 jaar. Bij 28 van de 61 langdurig opgenomen bewoners van verpleeghuis Topaz Overduin werd in bloedmonsters, verkregen tijdens om andere redenen geplande bloedafnames, de serumspiegel van 25(OH)D bepaald. De gemiddelde leeftijd van de deelnemers was 59 (42-76) jaar. 20 deelnemers (71%) kwamen meer dan 1x/week buiten en 10 deelnemers (36%) gebruikten voedingssupplementen met vitamine

D. De gemiddelde 25(OH)spiegel bedroeg 33 nmol/L (SD 15). 25 deelnemers (89%) waren vitamine D insufficient (25(OH)D < 50 nmol/L) waarvan 8 (29%) vitamine D deficiënt (25(OH)D < 25 nmol/L). 3 deelnemers (10%) waren vitamine D sufficiënt (25(OH)D > 50 nmol/L). Een positieve associatie met de mobiliteitsscore FAC (Functional Ambulation Classification) werd gevonden (p=0.023). Geconcludeerd wordt dat de prevalentie van vitamine D gebrek in deze over het algemeen jongere populatie verpleeghuisbewoners hoog is. Nog niet bekend is of vitamine D suppletie een positief effect zou kunnen hebben op het al bestaande hoge valrisico en/of de bij de ziekte van Huntington veel voorkomende neuropsychiatrische stoornissen.

In ***Hoofdstuk*** 7, de algemene discussie, worden de belangrijkste bevindingen van de in dit proefschrift besproken onderzoeken in een breder perspectief geplaatst, waarbij naast enkele methodologische overwegingen stil gestaan wordt bij de weerslag die de bevindingen zouden kunnen hebben op de dagelijkse zorgpraktijk.
Ook wordt in dit hoofdstuk voorgesteld verder onderzoek te doen naar:
- de veronderstelde extra winst in kwaliteit van leven bij verpleeghuisbewoners in geval van toepassing van UV-B bij de behandeling en preventie van vitamine D gebrek bij verpleeghuisbewoners (een onderzoeksprotocol is reeds opgesteld)
- de stand van zaken over ± 5 jaar, met betrekking tot bekendheid met, en draagvlak voor het vitamine D suppletieadvies voor ouderen van de Gezondheidsraad: herhaling van het enquête-onderzoek bij specialisten ouderengeneeskunde en huisartsen
- De meerwaarde van vitamine D oplaaddoseringen (snelle correctie van het vitamine D gebrek) bij verpleeghuisbewoners.
- de mogelijke effecten van vitamine D suppletie op het valrisco bij de ziekte van Huntington en de bij deze ziekte veel voorkomende neuropsychiatrische stoornissen (een concept onderzoeksprotocol is reeds opgesteld).

Algemene conclusies:
- De meeste verpleeghuisbewoners zijn vitamine D deficiënt of insufficiënt.
- De oudere huid is, ondanks de afgenomen capaciteit, zeer wel in staat om, onder invloed van UV-B licht, adequate hoeveelheden vitamine D te vormen.
- Behandeling van vitamine D gebrek door middel van de toepassing van UV-B, is bij verpleeghuisbewoners net zo effectief in het verhogen van de 25(OH)D serumspiegels en het onderdrukken van een secundaire hyperparathyreoidie als vitamine D suppletie per os.
- De toepassing van zonnebankbestralingen bij verpleeghuisbewoners liet zich in een pilot goed combineren met de dagelijkse zorg in verpleeghuizen. Het lijkt een goed alternatief te vormen, met mogelijk bijkomende positieve gezondheidseffecten, voor orale vitamine D suppletie in deze populatie.
- Er bestaan verschillende methoden voor het oraal suppleren van vitamine D. Dagelijks of wekelijks suppleren van vitamine D is effectiever met betrekking tot het bereiken van vitamine D sufficiëntie dan maandelijkse suppletie

- De adviezen van de Gezondheidsraad met betrekking tot vitamine D-suppletie bij ouderen worden in de praktijk onvoldoende opgevolgd door specialisten ouderengeneeskunde: Slechts ongeveer 25% van de bewoners van verpleeghuizen lijkt adequaat gesuppleerd te worden.
- De prevalentie van vitamine D deficiëntie en insufficiëntie is hoog bij een specifieke subgroep van, jonger dan gemiddelde, verpleeghuisbewoners: mensen met de ziekte van Huntington. Vitamine D suppletie is in deze groep is nog niet gebruikelijk.
  Het is nog niet bekend of ook in deze groep vitamine D gebrek geassocieerd is met een verhoogd valrisico en neuropsychiatrische stoornissen waarvan bekend is dat deze veel voorkomen bij de ziekte van Huntington.

Aanbevelingen:
- Omdat vitamine D suppletie effectief en mogelijk ook veiliger is, wanneer de toediening dagelijks of wekelijks plaatsvindt, verdient, in geval van orale vitamine D suppletie, deze methode aanbeveling bij geïnstitutionaliseerde ouderen.
- Omdat aangetoond is dat de prevalentie van vitamine D deficiëntie en insufficiëntie hoog is onder geïnstitutionaliseerde patiënten met de ziekte van Huntington, verdient het aanbeveling ook deze groep standaard, dagelijks te suppleren met 800 IE cholecalciferol.
- Om te komen tot een adequate vitamine D suppletie bij alle verpleeghuisbewoners is het wenselijk dat vitamine D suppletie standaard wordt opgenomen in alle zorg- en behandelplannen en dat het standaard suppleren van vitamine D in verpleeghuizen door de Inspectie voor de Gezondheidszorg (IGZ) beschouwd wordt als een norm en indicator voor verantwoorde en goede zorg.

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