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Review Article

The therapeutic effects of alfacalcidol on bone strength, muscle metabolism and prevention of falls and fractures

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Abstract

Established osteoporosis in older patients of both sexes is characterized by decoupled bone remodelling induced by sex hormone deficits and by somatopause, but also by lack of vitamin D and reduced synthesis of the D-Hormone (calcitriol; 1.25 $(OH)_2D$) in the kidneys and bone, as well as from lack of receptors and/or receptor affinity for D-Hormone in the target organs. Parallel to the decreased bone strength a loss of muscle power occurs, together with an increase in balance disorders and an increasing risk of "intrinsic", nonsyncopal locomotoric falls. In alfacalcidol therapy, D-Hormone is provided to the body in circumvention of its own regulation, by means of which higher hormone concentrations can be achieved in the target tissues than by administration of plain vitamin D. *In vitro* and *in vivo* experiments have provided growing evidence that D-Hormone analogs tend to normalize PTH, lead to an increase in the number and activity of osteoblasts, reduce the activity of osteoclasts, and might thus normalize the "high bone turnover" in elderly osteoporotic patients ("supercoupling"). In addition, it has been shown that D-Hormone analogs are able to increase muscle power and walking distance in elderly D-Hormone deficient patients. Besides the known effect on the vertebral fracture rate, new clinical data confirm that D-Hormone analogs might reduce peripheral fractures by reducing falls. The expanded understanding of the pathogenesis of glucocorticoid-induced osteoporosis with its disturbed calcium homeostasis and the pharmacological effects of alfacalcidol, which counteract such iatrogenic bone loss, contribute to the understanding of its clinical efficacy in this most frequent form of secondary osteoporosis. Due to its recently discovered immunomodulating properties, alfacalcidol might find a slot in the management of bone loss caused by chronic inflammatory diseases or by organ transplantations. Alfacalcidol has multifactorial effects, among which the best known are its anti-bone loss and anti-fracture efficacies in postmenopausal osteoporosis. This demonstrated efficacy is related to its involvement in bone remodelling, leading to an improved bone strength. Its mode of action on muscle power, which reduces falls, is unique, differentiating this form of therapy from all other anti-osteoporotic drugs, none having demonstrated any influence on falls.

Keywords: Alfacalcidol, Age-Related Osteoporosis, Glucocorticoid/Inflammation-Induced Osteoporosis, Falls, Fractures

Introduction

Greater life expectancy is an achievement of the modern era: however, longevity is inevitably accompanied by an increase in age-related diseases which consequently places a heavy burden on the healthcare system. An important member of this group of conditions is osteoporosis. In the elderly, however, a major factor contributing to fractures, in general, and to hip fractures in particular, is an increased tendency to fall which results from a variety of pathogenetic mechanisms that are set in motion by the ageing process, coupled with sundry drug therapies.

Fractures, especially hip fractures, are an extreme and ever-growing problem for patients with increased morbidity and mortality, for their families and for healthcare systems worldwide. Fear of breaking a hip, more than almost any other hazard of old age, haunts the elderly, since this event so often leads to loss of physical mobility and personal independence – and this fear is well-founded[1]. One challenge facing medical research today is to arrest the progressive trend in falls and in hip fracture incidence.

Primary osteoporosis in the elderly

Osteoporosis, with the main outcome problem of fractures, is a multifactorial disease characterized by low bone mineral density (BMD), decreased bone strength and neuromuscular deficiencies, resulting in increased risk of falls. Although bone mass is frequently considered to be the most important determinant of bone fragility, it explains only a part of the observed fracture risk. Clinical studies have demonstrated that less bone strength due to a prior fracture is a stronger predictor for future fractures than is low bone mass. With age the decline in bone strength is more pronounced than the decline in bone mass. The trabeculae become thinner, and a disruption of the trabecular network has been proven to be primarily caused by perforation of the horizontal supporting struts[2]. Bone strength results from a combination of bone turnover, bone mass, bone size, cortical thickness, trabecular architecture, microdamage accumulation, mineralization, quality of the material and osteocyte vitality.

Based on the "muscle ↔ bone" unit there is a positive correlation between neuromuscular deficiencies and BMD. Parallel to decreased bone strength, a loss of muscle power and performance (sarcopenia), neuromuscular deficiencies, deterioration in gait and postural stability occur. These deficiencies, together with slower response times lead to an increase of intrinsic, non-syncopal, locomotoric falls with no or only minimal contributions of external obstacles during normal daily activities. The changed type of falls, more often to the side instead of forward, and therefore, the direct impact of force on the hip together with the loss of soft tissue covering explain the sudden increase in hip fractures in elderly people over the age of 75[3].

Besides the described factors, malnutrition, co-morbidity and medications, especially those that have negative influence on neuromuscular co-ordination, also play a role. Other extra-skeletal factors are vision and cognitive impairments. A patient at high fall risk can be seen as an individual hosting a specific cluster of multiple fall risk factors.

Vertebral fractures can occur spontaneously and are pure osteoporotic fractures. Osteoporosis does not cause non-vertebral fractures, though it is one of the important risk factors. The exponential age-related increase of hip fractures is dramatically linked to the age-specific combination of an increased propensity to falls plus specific fall mechanisms, together with reduced bone strength.

In the light of the foregoing, the conventional diagnostic procedures for osteoporosis should be enlarged via fall risk assessment. Only then can the real risk of fracture be identified. The following independent risk factors for locomotoric falls should be investigated: muscle power/strength of lower extremities, postural competence/lateral balance, impairment of vision, taking multiple (>4) medications or taking certain groups of fall-inducing drugs, as well as cognitive impairment[3]. Muscle function and balance, both of which have been independently proven to be correlated to fall risk, can be measured, respectively, using the chair rising test and tandem manoeuvers[4,5].

As the structural changes can not be reversed, it is difficult to increase bone strength by therapeutic regimens. The focus should therefore be placed on prevention. Fall risk assessment and measures to improve the decreased muscle strength, the neuromuscular co-ordination and to avoid falls are also of great importance to prevent fractures.

Rationale for treatment with alfacalcidol

In the interest of achieving future optimal differential therapy, it seems to be important to differentiate between pure osteoporotic and more fall-related fractures. The slogan "No fall, no fracture" seems to be correct. Therefore, comprehensive programs aiming at the prevention of osteoporosis-related fractures should not only aim at increasing bone mass but also to significantly impacting on all other determinants of fracture risk.

Established osteoporosis in older patients of both sexes is characterized not only by decoupled bone remodelling induced by a deficit in sex hormones, as well as by a somatopause (insulin-like growth factor [IGF]-deficit), but also by a lack of vitamin D, a reduced synthesis of D-Hormone in the kidneys and bones and by a lack of receptors and/or receptor affinity for D-Hormone (VDRs) in the target organs. In principle, age-related sarcopenia is the consequence of a reduction of fast-twitch type II muscle fibres induced by decreased IGF-1 and increased cytokine levels, e.g., interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α). Increasing IL-6 and decreasing IGF-1 are synergistic factors for functional disability[56,67]. The presence of highly increased TNF-α levels in the muscle cells of the elderly is remarkable for future research[6]. Low D-Hormone and high PTH-levels also play important roles because proximal muscle weakness is a well-known clinical sign in hyperparathyroidism and disturbances in the metabolism of vitamin D in diabetes, chronic inflammatory diseases and reduced kidney function (creatinine clearance <65 ml/min). VDRs have been found in skeletal muscle and nerve cells. It has been recently confirmed in VDR gene-deleted mice that the absence of VDRs causes muscle abnormalities independently of secondary metabolic changes, e.g., hypocalcaemia or hyperparathyroidism, and that treatment with D-Hormone counterbalances the abnormalities in VDR-positive myoblastic cells and is necessary for an optimal muscle cell differentiation[57].

The individual and respective efficacies of native vitamin D compared to D-Hormone analogs in osteoporosis remain debated. The effect of vitamin D and calcium have been undoubtedly shown in patients with vitamin D deficiency, while the evidence supporting the efficacy of that treatment in vitamin D-replete subjects remains limited. Currently, supplementation with plain vitamin D is not considered as a pharmacological therapy, but as a dietary substitute. Due to the feedback-regulation of the final activation-step of 25-hydroxyvitamin D (25(OH)D) in the kidneys into the active

hormone 1,25-dihydroxyvitamin D (calcitriol, D-Hormone), oral supplements of plain vitamin D have a limited ability to increase the D-Hormone level[7,8]. That means that in vitamin D-replete patients, therapeutic effects on bone, muscle or other target organs have better chances to be achieved using D-Hormone analogs. D-Hormone deficient patients (inhibition of 1-alpha-hydroxylase in the kidney), e.g., elderly patients, patients with decreased kidney function, nephropathies, hypertension or patients with chronic inflammatory diseases (rheumatoid arthritis, Crohn's disease, chronic obstructive lung diseases), type 1 diabetes, arteriosclerosis and heart failure) are likely to be resistant to plain vitamin D treatment. The same pattern can also be found in patients with a lack of receptors or less receptor affinity for D-Hormone (VDR deficits) in the target organs, e.g., GI-tract, bones, muscles, in old age or by high glucocorticoid therapy[7,8]. Alfacalcidol is activated in the liver and in other target organs like bones and is a so-called prodrug of the D-Hormone. The D-Hormone deficiency can be treated by bypassing the body's own regulation in the kidneys[7,8]. No harmful D-Hormone levels can be found in the serum, because of the direct binding of the D-Hormone to the receptors of the target organs. This is one of the reasons for the low observed rates of hypercalcaemia in clinical trials on D-Hormones. The vitamin D resistance based on VDR-deficits may also be corrected using D-Hormone analogs through their influence on the expression and activation of VDRs[9].

Alfacalcidol induces active absorption of calcium and phosphate, improves mineralization of the skeleton and facilitates normal neuromuscular functioning. The most important endocrine regulator of PTH is the D-Hormone. D-Hormone analogs indirectly suppress PTH, which is commonly high in elderly patients, through increased calcium absorption. The D-Hormone directly suppresses PTH by inhibiting the proliferation of the parathyroid gland through the induction of apoptosis, as well as by reducing PTH synthesis and release. The reduced effects of PTH on bone are also of importance. D-Hormone also reduces the release of pro-inflammatory cytokines, which are partly increased in the elderly and are factors for osteoclast activation and bone resorption, but also for muscle wasting[6,10,66,72]. It is unclear to what extent the impairment of the immune system due to increased pro-inflammatory cytokine levels and decreased suppressor cells is responsible for age-related bone loss and muscle weakness, however, the positive effect of alfacalcidol on regulating the cytokine homoestasis and increasing suppressor cells has been positively recognized[18,37-43].

D-Hormone inhibits 1-α-hydroxylase and stimulates 24-hydroxylase which leads to increased formation of $24,25(OH)_2D$. The latter is a metabolite that is apparently important for healing of microfractures and microcallus formation, thus contributing to bone strength[73]. There is preliminary evidence of an anabolic effect of this compound on the skeleton[11,12,74,75]. D-Hormone increases the synthesis of transforming growth factor(TGF)-β and IGF-2, and increases the number of IGF-1 receptors. These effects stimulate osteoblast proliferation and differentiation. The in vitro and in vivo increased synthesis of collagen type I and matrix proteins, such as osteocalcin and osteopontin, which are important for mineralization, functioning and metabolism of bone tissue, are additional explanations for the influence on bone strength[9,10].

In the ovariectomized rat model of osteoporosis there is histomorphometric and biochemical evidence that oral administration of alfacalcidol causes dose-dependent suppression of osteoclastic bone resorption, as opposed to well-known in vitro "stimulation". The direct inhibition of D-Hormone analogs on bone resorption (thus not mediated by PTH reduction) can be explained based on the new findings that alfacalcidol inhibits osteoclastogenesis in vivo by decreasing the pool of osteoclast precursors in bone marrow[54,76]. Unlike typical inhibitors of bone resorption such as estrogens and bisphosphonates, alfacalcidol does not suppress, but rather stimulates bone formation, e.g., alfacalcidol may be able to "supercouple" these two processes[11]. Shiraishi et al. analyzed the mechanical bone strength of 8-months-old ovariectomizied rats at the femur with a three-point bending test and at the vertebral body specimens using a compression test. In that study, alfacalcidol increased BMD and bone strength more effectively than plain vitamin D did while allowing for similar levels of effect on calcium absorption[12]. These advantageous results of alfacalcidol on bone microstructure have been confirmed by micro-CT scanning[13]. It has also been proven in parathyroidectomized rats under constant PTH infusion that alfacalcidol exerts a direct anabolic effect on bone mass and strength independent of calcium absorption and PTH suppression[76].

D-Hormone analogs are thus promising candidates for a pharmacological intervention with positive effects on muscle function and postural capacity and falls. D-Hormone regulates the calcium metabolism in muscles and the control of muscle contraction and relaxation[58]. Indeed, D-Hormone receptors have been recently found on skeletal muscle cells[14]. Older age is significantly associated with decreased VDR expression in human skeletal muscle tissue[59]. These observations suggest that the age-related decline in muscle strength and function and related increase in falls could be partly explained by a decrease of VDR's number or affinity and/or a decrease of D-Hormone in serum. As a matter of fact, a positive correlation was found between muscle strength, function, and D-Hormone serum levels in the elderly[15,60]. There is current clinical evidence that alfacalcidol improves muscle function. Histochemical classification based on muscle biopsies of the fibre composition revealed that a treatment of osteoporotic patients with 1 mcg alfacalcidol daily for 3 to 6 months induced an increase in the relative number of fast-twitch type II A fibres accompanied by a reduction of fast twitch type II B fibres. The cross-sectional area of the fast twitch type II A fibres also increased[16]. The time taken for people to get dressed was significantly less after treatment[16]. The serum concentrations of calcidiol (25(OH)D) were constant during the study. Alfacalcidol

Table 1: Rationale for treatment of sarcopenia in old age with D-Hormone analogs (Alfacalcidol)

- Muscle and nerve cells do have D-Hormone Receptors (VDRs)
- VDRs in muscle cells are decreasing with age
- VDR gene-deleted mice develop smaller muscle fibers based on impaired muscle cell differentiation
- D-Hormone counterbalance these abnormalities in myoblastic cells
- Treatment with Alfacalcidol increases the ratio of Fast Twitch Type II muscle fibers in the elderly
- D-Hormone regulates the calcium metabolism in muscles (control of muscle contraction and relaxation)

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Table 1.

improved muscle strength (isometric knee extension strength) and functional ability (walking distance over 2 minutes) significantly after 6 months of treatment in elderly D-Hormone deficient women[17]. Patients with rheumatoid arthritis, osteopenia and normal vitamin D levels (49-59 nmol/l), who received a daily dose of 1 mcg of alfacalcidol showed a significant increase in muscle power (60 percent), as compared to only an 18 percent increase in those patients who received a daily dose of 1000 IU of plain vitamin D[18].

The rationale for treatment of sarcopenia in old age with alfacalcidol is given (Table 1). The key question, based on the described pharmacologic effects in pilot studies, is, whether and to what extent alfacalcidol can reduce falls and fractures in prospective, double-blind, placebo-controlled studies.

In a prospective study 489 osteopenic women, aged 65-77 years with normal calcidiol serum levels (25(OH)D=77.5 nmol/l), were randomized in a double-blind trial using treatment with a placebo, calcitriol 0.25 mcg twice daily, conjugated equine estrogens (CEE) 0.625 mg (ERT or HRT) daily and a combination of CEE and calcitriol[19]. The cumulative number of falls in each group was 63 percent taking the placebo, 56 percent taking estrogen, 56 percent taking the combination of estrogen and 48 percent taking calcitriol, the decrease in the number of falls in the D-Hormone treated group being highly significant (p<0.001). The three-year incidence rate for falls was 0.43 on placebo, 0.39 on ERT/HRT, 0.35 on the combination and significantly lower on calcitriol 0.29 (p<0.001). There was a significant reduction in fall-related fractures in the groups treated with calcitriol, as compared to the non-calcitriol groups[20].

378 Swiss community-dwelling women (n=191) and men (n=187), averaging 75 years of age, were randomized to receive in a double-blind trial either 1 mcg alfacalcidol or a placebo daily for 9 months. Falls and dietary calcium intake were assessed using questionnaires. Baseline calcidiol and calcitriol serum levels were within the normal ranges. When compared to the group taking the placebo, those being treated with alfacalcidol had a significant reduction both in the number of fallers (OR 0.45; 95 percent CI 0.21-0.97, p=0.04) and in the number of falls (OR 0.46, 95 percent CI 0.22-0.99, p=0.045) of participants with a total calcium intake of more than 500 mg calcium[21].

Impaired renal function is detrimental to the activation of D-Hormone. Dukas et al. found in multivariate-controlled analyses in elderly women and men over the age of 70, that a creatinine clearance (CrCl) of <65 ml/min is significantly associated with low D-Hormone serum levels and with a significant four times increased risk of falls compared to participants with normal CrCl[61]. Thirty-six weeks of treatment with alfacalcidol (1 μg daily) significantly and safely reduced in community-dwelling elderly men and women with a CrCl of <65 ml/min the low CrCl associated high risk of falls by -71%[61].

A recently published meta-analysis on the effect of vitamin D on falls included a sub-group analysis to differentiate between the effect-sizes of plain vitamin D and D-Hormone analogs[62]. For 3 studies involving 613 participants treated with cholecalciferol, the corrected OR of falling was 0.83 (95% Cl, 0.65-1.06). In contrast, the reduction of fallers was statistically significant based on two studies involving 626 patients treated with D-Hormone analogs (OR 0.71, 95% Cl,

Table 2: Plain Vitamin D or "Active" D-Hormone analogs (Alfacalcidol)?

Plain Vitamin D

- Nutritional substitution
- Only effective in patients with vitamin D deficiency (25(OH)D < 30 nmol/l or < 12 ng/ml)
- In vitamin D replete patients no further increase of 1,25(OH)$_2$D (Calcitriol; D-Hormone) based on strict body-own regulation in the kidney takes place
- Patients with D-Hormone deficiency (inhibition of 1α-Hydroxylase) and/or D-Hormone Receptor (VDR) deficit in quantity and quality are resistant to plain vitamin D

Alfacalcidol

- Pharmacological treatment (not only active in renal dysfunction!)
- Prodrug of Calcitriol (D-Hormone), will be activated in liver and in bone
- Increase of D-Hormone in target organs (not in serum!) in vitamin D deplete, but also in replete patients
- Resulting increase of D-Hormone decreases PTH, normalizes bone remodeling and increases bone strength, increases muscle strength and neuromuscular coordination, reduces falls and fractures
- D-Hormone deficiency can be treated by bypassing the body-own regulation in the kidney
- Vitamin D resistance can be effectively treated by counterbalancing the VDR deficit and by inducing VDRs in different target organs

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Table 2.

0.55-0.92). It is worth mentioning that most participants in the plain vitamin D group have been vitamin D-deficient in comparison to the participants treated with D-Hormones, which had normal serum vitamin D levels.

In general, alfacalcidol was able to reduce the non-vertebral fracture rate significantly[33]. The rate of hip fractures was reduced in stroke patients after only six-months treatment with a daily dose of 1mcg alfacalcidol[22] and after 18 months of dosing elderly patients with Parkinson's disease[23] with 1 mcg of alfacalcidol, the rate of hip fractures was also reduced, i.e., in patients with a high risk of falls. Raloxifene and bisphosphonates (alendronate, risedronate) and estrogens, based on clinical trials, do not provide clear demonstration of their efficacy on the reduction of the rate of falls[24,25]. The dual efficacy of D-Hormone analogs on bone and muscle and, subsequently, on falls and osteoporosis-related fractures, can therefore be considered as unique.

It is important to recognize, that the positive effects of alfacalcidol and calcitriol on the muscle fibre type II, the daily living activities of the elderly, muscle strength in patients with rheumatoid arthritis and, especially, on the reduction of falls in elderly women and men were not due to the correction of age-related vitamin D deficiency, as in some other studies, because most of the patients had normal vitamin D serum levels at baseline. D-Hormone analogs acted as pharmacological treatments by increasing the levels or the action of D-Hormone in the target organs, muscles and/or nerves.

In addition to pharmacological treatments aimed at limiting falls and strengthening bones, we have also to look for

adequate exercise. The deterioration of locomotoric and balance functions associated with advancing age can be counteracted by muscle, gait and balance training. Tai Chi and balance programs have been proven effective in reducing the frequency of falls[26]. We should also minimize using fall-related drugs like neuroleptics, benzodiazepines, tricyclic antidepressants and glucocorticoids. For a person at high risk of falling hip protectors should be used.

D-Hormone analogs have been proven to be active in increasing BMD and in reducing vertebral and non-vertebral fractures in several prospective, randomized, mainly placebo-controlled studies[22,23,27-29] and by an epidemiological prospective cohort study[30]. A recently published meta-analysis conducted by two independent research groups from the USA ("The Osteoporosis Methodology Group") and Canada ("The Osteoporosis Research Advisory Group"), clearly showed the advantageous efficacy of "hydroxylated vitamin D" (alfacalcidol, calcitriol) versus plain vitamin D[31]. D-Hormone analogs had a consistently larger impact on BMD than did plain vitamin D. The difference between the groups was statistically significant for total body ($p < 0.03$) and for combined forearm ($p < 0.01$) after the final year of treatment. Direct and indirect evidence suggest that D-Hormone analogs may prevent vertebral fractures (Relative Risk RR=0.64; 95 percent CI 0.44-0.92) to a larger extent compared to treatment using plain vitamin D[31,63,68].

The decrease of risk of vertebral fractures by using D-Hormone analogs is in the range of bisphosphonates or raloxifene. The number needed to treat (NNT), e.g., the number of patients, that have to be treated for two years to prevent one vertebral fracture is not different when using D-Hormone analogs (NNT=94) in comparison to other anti-osteoporotics, e.g., risedronate (NNT=96), alendronate (NNT=72), or raloxifene (NNT=99), as shown in a summary of meta-analyses[32].

A second meta-analysis confirmed the effects on bone mass and, very importantly, the decrease in the vertebral fracture risk by D-Hormone analogs (RR=0.53; 95 percent CI 0.47-0.60)[33]. In this meta-analysis a reduction of non-vertebral fractures (RR=0.34; 95 percent CI 0.16-0.71) was proven. The fact that two independent meta-analyses showed similar results is very strong additional proof of the efficacy of D-Hormone analogs in the reduction of vertebral fractures.

In a recent comparative meta-analysis, Richy et al. confirmed that D-Hormone analogs exhibit better efficacy in preventing vertebral bone loss and vertebral and non-vertebral fractures compared to plain vitamin D in postmenopausal osteoporosis[63].

A majority of data demonstrated the efficacy of D-Hormones on bone loss and fall and fracture prevention in postmenopausal/age-related osteoporosis coupled with a very low rate of side effects. In this setting, a post-marketing surveillance study on 13,550 osteoporotic patients showed 1.1% side effects, including only 0.22% patients with hypercalcaemia without kidney stone[77]. Hypercalcemia could be completely avoided by checking the serum calcium levels at the beginning and then all 3-6 months after commencement of therapy.

In future a clear differentiation should be made between supplementation using calcium and plain vitamin D in very old, vitamin D-deficient women and men (>75 years), and the pharmacological treatment of patients with established osteoporosis using D-Hormone analogs, independent of the patients' vitamin D status[64] (Tables 2 and 3).

Glucocorticoid/inflammation-induced osteoporosis

Glucocorticoids (GC) are widely used in clinical practice and play a major role in the treatment of a variety of chronic diseases. Despite their indisputable therapeutical advantages, long-term glucocorticoid treatment is often overshadowed by severe side-effects that sometimes may produce morbidity comparable to that of the original illness. One of these side effects is the development of osteoporosis, which is known to occur as a consequence, not only of chronic oral GC-administration, but also due to the deleterious effects of the underlying disease on bone metabolism. Bone loss is highest in the initial months of therapy, and the fracture incidence of glucocorticoid-induced osteoporosis (GIOP) is estimated to be between 30 and 50 percent among patients receiving this type of treatment over a long period of time. This high fracture rate cannot be explained by the respective loss of bone mineral density alone. It is suggested, therefore, that early negative influences on bone strength contribute to this rapid increase in bone fragility.

It is well established that glucocorticoids affect bone through multiple mechanism pathways. Pathophysiological effects of glucocorticoids on bone and calcium homeostasis include decreased intestinal calcium uptake, increased renal excretion of calcium, impairment of osteoblast function, promotion of osteocyte apoptosis, increased osteoclastic bone resorption and myopathy. In addition, glucocorticoids inhibit the favorable effects of sexual and growth hormones on bone. It has recently been recognized that the expression of D-Hormone receptors (VDRs) was inhibited[34]. There is general consensus that pro-inflammatory cytokines (e.g. IL-1, IL-6, IL-12, TNF-α) induce bone resorption in chronically inflammatory diseases. There are however new findings showing that cytokines like TNF-α also interfere with bone formation. The increase of muscle weakness and falls induced by glucocorticoids and cytokines are features that have been underestimated[6,52]. High doses of GCs result in decreased IGF-1 and IGF-2 expression and this accounts for the atrophy of the diaphragm muscle[65]. TNF-α and other cytokines, such as IL-1 and IL-6, induce muscle proteolysis and are involved in muscle wasting[66]. GCs and cytokines interfere directly with the IGF-1 signalling pathway[67]. Recent work demonstrate upregulation of myostatin, a negative regulator of muscle mass by GCs[69]. Especially the facts, that the incidence of falls and non-vertebral fractures increase rapidly after the first 3 months and revert sharply towards baseline levels after discontinuation of oral GC treatment, are very important in prevention and treatment strategies[52].

Table 3: Hypothesis
Low D-Hormone Syndrome – Falls and Fractures

- Elderly women and men with CrCl < 65 ml/min and reduced VDRs in muscle
- Chronic inflammatory diseases (RA, IBD, COPD) with increased cytokine levels and GC-treatment (VDRs ↓)
- Patients after organ transplantation with low CrCl (Cyclosporin A) and increased cytokine levels
- Diabetes and/or heart failure with increased cytokine levels and low CrCl

Alfacalcidol reduces the Low D-Hormone Syndrome induced high risk of falls and fractures

Table 3.

Rationale for prevention and treatment with alfacalcidol

Recent evidence suggests that deleterious pharmacological effects of glucocorticoids on bones or muscles may be counteracted by the use of D-Hormone analogs[10]. Experimental data suggest that TNF-α inhibits renal 1-alpha-hydroxylase and therefore activation of vitamin D in target organs[35]. This is in accordance with clinical findings that inflammatory diseases are associated with low serum D-Hormone levels depending on disease activity[36]. This D-Hormone deficiency could be treated with D-Hormones, but not with plain vitamin D. The same is true for the reduction of D-Hormone receptors (VDRs) induced by glucocorticoids, because D-Hormone analogs provide the target organs with sufficient levels of D-Hormone to activate VDRs. It is also important to know that D-Hormone protects osteoblasts *in vitro* against TNF-α-induced apoptosis. This mechanism has been demonstrated *in vivo* in the inflammation-mediated osteopenia (IMO) model, an animal model that simulates bone loss in rheumatoid arthritis[37]. D-Hormone analogs have very specific T-cell immunoregulating properties, which produce tolerogenic antigen-presentating cells, decrease T-helper cells, increase suppressor cells and induce cytokine homeostasis by decreasing pro-inflammatory and increasing anti-inflammatory cytokines[38,39]. These effects have been proven in several autoimmune disease models[40,41].

With regard to the immunomodulating properties several questions still need to be answered. Can D-Hormone analogs be used as adjuvant therapy to disease modifying therapy in autoimmune diseases which have been shown in pilot studies[42,43]? Are these effects responsible for the special efficacy in organ transplantation-induced osteoporosis? Can the risk of hypercalcemia using higher dosages of D-Hormone analogs be reduced by using a combination therapy with bisphosphonates[53]? The previously unrecognized partly immune-mediated mechanisms of D-Hormone deficiency in human diseases, like age-related osteoporosis and muscle weakness with increased risk of falls, chronic inflammatory diseases, renal insufficiency, diabetes, hypertension, arteriosclerosis and heart insufficiency reflect the importance of higher levels of D-Hormone at target organs using treatment with D-Hormone analogs.

There is another very important open question. Are D-Hormone analogs able to reduce falls in GC-treated patients as it has been proven in the elderly[20,21,61]? The correlation vis-à-vis the risk of falling between elderly patients and GC-treated patients are the decreased D-Hormone levels and reduced number of VDRs in target tissues and increased levels of PTH and cytokines in the serum of both groups[9,10,59].

Plain vitamin D is fully active in patients with vitamin D deficiency, which is less frequent in younger patients with chronic inflammatory diseases and glucocorticoid treatment. In a double-blind, placebo-controlled study the effects of 50000 IU vitamin D weekly in combination with 1 g calcium daily for the prevention of glucocorticoid-induced osteoporosis were investigated[44]. After three years intention-to-treat analysis revealed no significant differences between the vitamin D/calcium and the placebo groups regarding the prevention of vertebral bone density.

Alfacalcidol and calcitriol based on the described pathogenesis of GIOP/inflammation-induced bone loss and fractures, have demonstrated their usefulness in the therapy of GIOP. In animal trials alfacalcidol increases bone strength more effectively than plain vitamin D[12]. This is important based on the described early decrease of bone strength in this type of osteoporosis. All clinical studies with these agents in GIOP have shown an increase or a stabilization of BMD in comparison to control groups. Some studies that examined the prevention of GIOP by using alfacalcidol in patients with different underlying diseases demonstrated the inhibition of bone loss, even in cases of very high doses of GCs[45,46]. 145 patients requiring more than 30 mg prednisolone daily were randomized by Reginster et al. into two groups: a treatment group receiving alfacalcidol 1 mcg daily for a year (n=74) and a placebo group (n=71)[45]. The two groups did not differ in demographic, biochemical and/or clinical parameters. Even the daily glucocorticoid dose was similar (alfacalcidol group: mean 46.6 mg/day; placebo group: 46.3 mg/day). The mean changes in BMD after 12 months were +0.4 percent in the alfacalcidol-treated group as opposed to –5.7 percent in the placebo group (p=0.02). It is worth mentioning that the glucocorticoid dose did not differ significantly between the groups at any time during the entire observation period. There were no differences in serum calcium concentrations observed between the groups.

The relative efficacies of alfacalcidol and etidronate in patients after cardiac transplantation undergoing therapy with GCs and cyclosporine A, have also been investigated. The authors showed a better efficacy on BMD in the alfacalcidol group both at the lumbar spine and the femoral neck as compared to the etidronate group. More fractures were found in the etidronate than in the alfacalcidol group[47]. This result has to be interpreted with caution, as only very few fractures had occurred. Similar results were obtained in a study in which patients with cardiac or lung transplantations were studied[48], and calcitriol significantly reduced the number of vertebral fractures. A more recent study confirms these findings. A one-year double-blind trial compared 149 patients (122 women, 27 men) randomized to alendronate 10 mg daily or calcitriol 0.5 μg daily versus 27 control subjects concurrently transplanted, but not randomized. The change in spinal BMD was -0.7% with alendronate, -1.6% with .and -3.2% in controls. Among the patients in the calcitriol group who adhered to therapy, the BMD decreased only by 0.5%. The change in femoral neck BMD was -1.7% with alendronate, -2.1% with calcitriol and -6.2% in controls. Urinary NTX fell by 34% with alendronate, 26% with calcitriol but were unchanged with controls. By six months, the serum parathyroid hormone level had decreased in the calcitriol group and had increased in the alendronate group. New vertebral fractures occurred in 6.8% of alendronate subjects, 3.6% of subjects treated with calcitriol and 13.6% of controls[49].

Surprisingly new data suggest that D-Hormones have a synergistic immunomodulatory effect in combination with routine therapy for immunosuppression, reducing the doses of potent, but toxic and expensive cyclosporine and glucocorticoids required to prevent organ rejection without any detectable change in episodes of rejection, infection or deaths[70].

Additionally, in two new meta-analyses treatment with D-Hormone analogs has been proven to maintain statistically significant bone mass in six and eleven clinical trials, respectively with patients using glucocorticoids[33,71]. The recently published one showed also the significant reduction of the vertebral fracture rate using D-Hormone analogs in GIOP compared with no treatment, placebo, plain vitamin D and/or calcium[71].

Taken together, there is very good evidence that treatment with D-Hormone analogs is also able to maintain bone mass in patients taking very high doses of GCs. This fact is taken into consideration in the guidelines of the American College of Rheumatology[50].

A study compared the effects of plain vitamin D and alfacalcidol in patients with rheumatoid arthritis (RA). Seventy-one patients with RA, whose mean age was 65, who had osteopenia (T-score <-1) and normal vitamin D serum levels were included[18]. After randomization, patients received either vitamin D (1000 IU/day) or alfacalcidol (1 mcg/day) for four weeks. Additionally, all patients received calcium (500 mg/day). After 4 weeks there was shown to be a significantly more positive influence of alfacalcidol on the decrease of urinary bone resorption marker N-terminal telepeptides of collagen type I (NTX), as well on PTH (group difference p<0.003 and p<0.002). A significant decrease of pain score occurred only in the alfacalcidol group (<0.001). This effect can be related to the observed reduction of tumour necrosis factor (TNF)-α (p<0.05) only with the use of alfacalcidol. In patients receiving alfacalcidol, muscle power increased significantly (groups difference p<0.05). There also could be a correlation to the reduction of TNF-α, because TNF-α is a known factor in muscle atrophy[6,66]. Alfacalcidol may be an important treatment option in secondary osteoporosis based on inflammatory rheumatic diseases[18].

The data of another study compared calcitriol (0.5-0.75 μg daily), simple vitamin D (30000 IU weekly+600 mg calcium daily) with alendronate (10 mg+600 mg calcium daily) in the prevention and treatment of glucocorticoid-induced osteoporosis and did not suggest any difference between vitamin D and calcitriol, but, after 2 years it did show a significant superiority of alendronate on vertebral BMD[55]. These results have to be interpreted with great caution, because the mean daily GC doses at the commencement and the cumulative GC doses during the study were statistically significantly higher in the calcitriol group than in the other two groups. The efficacy of calcitriol has been, of course, negatively affected by this bias and by the fact that there was no supplementation of calcium in this group. In addition baseline lumbar BMD was significantly higher in the alendronate group. Another concern is the unknown toxicity of such high dosages of plain vitamin D over a long period of time.

The aim of a recently presented study was to compare the therapeutic efficacy of alfacalcidol with plain vitamin D in

patients with established glucocorticoid-induced osteoporosis[51]. Patients on long-term GC therapy were included as matched-pairs to receive randomly either 1 mcg alfacalcidol plus 500 mg calcium per day (group A, n=103) or 1000 I.U. vitamin D plus 500 mg calcium (group B, n=101). The two groups were well matched in terms of age, sex ratio, mean height and weight, daily dosage and duration of GC-therapy and the percentages of the three included underlying diseases. During the three-year study a median increase of BMD at the lumbar spine of 2.4 percent in group A as compared with loss of 0.8 percent in group B was observed (p<0.0001). The 3-year rate of patients with at least one new vertebral fracture was 9.7 percent among those assigned to the alfacalcidol group, as compared to 24.8 percent among those assigned to the vitamin D group (Risk Reduction: 0.61; 95 percent CI 0.24 to 0.81; p=0,005). In accordance with the observed fracture rate, the alfacalcidol group showed a substantially larger decrease in back pain than the plain vitamin D group (p<0.0001). Generally, side effects in both groups were mild and only 3 patients in the alfacalcidol group and 2 patients in the vitamin D group had moderate hypercalcemia. The authors concluded that alfacalcidol plus calcium is highly superior to plain vitamin D_3 plus calcium in the treatment of established osteoporosis.

Due to the pleiotropic efficacy on bone, muscles and the immune system the physiological alfacalcidol is an important treatment option for patients with glucocorticoid/inflammation-induced osteoporosis.

Summary and prospects

In our growing fervour to increase bone mineral density with continuously improved techniques, physicians have often underestimated other important dimensions related to fracture risk, e.g., bone strength. Some important characteristics of ageing people, as decreased muscle performance and balance disturbances and, consequently, an increased risk of falls have been nearly totally neglected. The holistic analysis of the interactions between organs, muscles and bones, is now in the focus of modern and future research.

Multifactorial interventions on muscle power and balance training together with a single or a combination of specific pharmacological therapy(ies) will gain importance in the future. D-Hormone analogs, e.g., alfacalcidol, have shown promising effects on bone remodelling and bone microarchitecture. High quality studies in PMOP have shown that they were able to prevent bone loss and fractures at the spinal level at a greater extent compared to vitamin D. D-hormone analogs are also able to prevent bone loss at the hip level and prevent non-spinal fractures at a greater extent compared to native vitamin D. In GIOP, D-Hormone analogs are able to limit bone loss at the spine and, less markedly at the hip level, while more research is needed to clearly assess their long-term anti-fracture properties. In this way, D-Hormone analogs are interesting candidates for a pharmacological improvement of bone strength and the prevention of osteoporotic fractures. The multifactorial effects on muscle functions, neuromuscular co-ordination with the important consequence of reduction of falls and fall-related fractures may be unique, and thus differentiate this form of therapy from all other anti-osteoporotic drugs. Furthermore, the fact that D-Hormone analogs have implications in the modulation of immunity and cytokine homeostasis may lead to critical applications in the near future. Future research is, and will be, progressively concentrated on the challenge of determining whether cytokine regulation by D-Hormone analogs is responsible for improvement of muscle function, pain relief in chronic inflammatory diseases, and/or for positive effects observed in autoimmune diseases, e.g., rheumatoid arthritis or multiple sclerosis, arteriosclerosis, and congestive heart failure.

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