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ORIGINAL ARTICLE

Alfacalcidol improves muscle power, muscle function and balance in elderly patients with reduced bone mass

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Abstract We investigated the effect of daily therapy with 1 mcg alfacalcidol (Doss®-TEVA/AWD-pharma) on muscle power, muscle function, balance performance and fear of falls in an open, multi-centered, uncontrolled, prospective study on a cohort of patients with reduced bone mass. Among the 2,097 participants, 87.1% were post-menopausal women and 12.9% were men. Mean age was 74.8 years and mean body mass index (BMI) 26.3 kg/m^2. A total of 75.3% of the study population had osteoporosis, 81% a diagnosis of "increased risk of falls" and 70.1% had a creatinine clearance (CrCl) of <65 ml/min. Participants underwent muscle function and muscle power tests at onset and after 3 and 6 months: the timed up and go test (TUG) and the chair rising test (CRT). At baseline and after 6 months, participants performed the tandem gait test (TGT) and filled out a questionnaire evaluating fear of falling. Successful performance in the muscle tests is associated with a significantly lower risk of falls and non-vertebral fractures in elderly patients (successful test performance: TUG $\leq$ 10 s (sec), CRT $\leq$ 10 s, TGT $\geq$ 8 steps). A significant improvement in the performance of the two muscle tests was proved already after 3 months of treatment with alfacalcidol and further increased by the end of the therapeutic intervention. There were significant increases in the number of participants able to successfully perform the tests: 24.6% at baseline and 46.3% at the end of trial for the TUG ($P < 0.0001$) and 21.7% at baseline and 44.2% at the end for the CRT test ($P = 0.0001$). The mean time used for the TUG was decreased by 3.0 s from the average onset value of 17.0 s and by 3.1 s from the initial average 16.5 s for the CRT. The percentage of participants able to perform the balance test (TGT) increased from 36.0% at onset to 58.6% at the end of the trial ($P < 0.0001$). An increased fear of falling was reduced by the end of the study in 74.4% of the patients. Throughout the study, there were 26 adverse drug reactions in 11 out of 2,097 patients (incidence 0.52%). No serious adverse drug reactions and no cases of hypercalcemia were documented. We conclude that treatment with alfacalcidol is safe, increases muscle power, muscle function and balance and reduces fear of falls. The significant improvement in the three muscle and balance tests and fear of falls may have a preventative effect on falls and fractures. We suggest that the quantitative risk tests used in this study could be reliable surrogate parameters for the risk of falls and fractures in elderly patients.

Keywords Alfacalcidol · Muscle · Balance · Fear · Falls · Fractures

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Introduction

There is increasing evidence that among older people, falls, not osteoporosis, are the strongest risk factor for fractures [1]. Falls are among the most common and serious problems facing the elderly. Falling is associated with considerable morbidity, reduced functioning, premature nursing home admission and mortality [2].

Older individuals are at an increased risk of falls mainly due to an age-related increase in muscle weakness and

decreased balance, as well as the accumulation of impairments and co-morbidities observed with aging [2–4]. Clinical experience and epidemiological data demonstrate that mobility is a key determinant of successful aging and quality of life in old age. Loss of mobility is one of the most prominent threats in old age [4]. Fear of falls and "post-fall anxiety syndrome" are today well recognized as frequent consequences of falls. The loss of self-confidence to move safely can result in self-imposed functional limitations [2]. As shown in several studies, therapy with vitamin D, alfacalcidol or calcitriol [5–9] significantly reduces the frequency of falls. This may be explained by the fact that D-hormone (calcitriol) has been shown to be important for the maintenance of muscle strength, muscle function and balance in older individuals [10, 11]. Growth of muscle cells and the differentiation of muscle fibers are D-hormone-dependent, and D-hormone acts through a highly selective D-hormone receptor directly on myocytes [12, 13].

The serum levels of D-hormone however are dependent on creatinine clearance [14]. A creatinine clearance of <65 ml/min. is already associated with decreasing serum levels of calcitriol and an increased risk of falls and osteoporotic fractures [15–18]. Consequently, a creatinine clearance of <65 ml/min is associated with significant lower muscle power and balance [19].

In this study, we investigated the effect of daily therapy with 1 mcg alfacalcidol for 6 months on muscle power, muscle function, balance and fear of falls in elderly German patients with low bone mass (75% with osteoporosis), with reduced creatinine clearance (70% with CrCl < 65 ml/min) and diagnosed with the "Esslinger Fall Risk Assessment" [4] (81% with an increased risk of falls).

The scientific question was whether it is possible to improve muscle weakness, decreased balance and increased fear of falls by a pharmacological treatment such as alfacalcidol [20, 21].

Subjects and methods

This open, uncontrolled, prospective study on a cohort of elderly patients ($n = 2097$) with low bone mass was conducted from July 2007 until November 2008 with the aim of assessing the effect of daily therapy with 1 mcg alfacalcidol on muscle power, muscle function, balance performance and fear of falls. None of the patients had been treated before with alfacalcidol. GPs, internists and orthopedists ($n = 977$) from allover Germany with experience in the management of osteoporosis were asked to fill in a questionnaire on their patients, to have their patients perform different muscle and balance tests, to measure several basic laboratory values and to document side effects.

The questionnaire had to be completed at the beginning, after 3 and 6 months or at the end of observation. Information on gender, age, weight, height, BMI, diagnosis and type of osteoporosis, fear of falls and limitations in household and outdoor activities (using a 5-point score of none, very low, same, strong and very strong), estimation of risk of falls in elderly patients based on the "Esslinger Fall Risk Assessment" [4], renal function, co-medication, concomitant diseases, muscle and balance training, and an estimation on efficacy and safety of treatment, adverse events and patient satisfaction was documented.

Furthermore, laboratory tests were performed measuring serum creatinine (creatinine clearance CrCl calculated with the Cockcroft–Gault formula) [22] and calcium in serum. Diagnostic criteria for osteoporosis used by individual physicians were not re-assessed, i.e. diagnosis of osteoporosis is based on physician reports.

Functional assessment

The main outcome of the analysis of this open, prospective trial was the influence of a daily therapy with 1 mcg alfacalcidol for 6 months on functional mobility and balance measured by the timed up and go test (TUG), the chair rising test (CRT) and the tandem gait test (TGT). These tests are in line with the official German and international guidelines for the assessment of patients' risk of falls [2, 23, 24].

The TUG test is a measure of functional mobility, muscle function, gait speed and balance [25]. The concept is appealing, because it describes a realistic mobility assessment including potential fall situations, such as getting in and out of a chair, walking and turning around. The person is observed and timed while rising from an arm chair (seat height 48 cm; arm height 68 cm), walking 3 meters at a normal speed, and going around an obstacle on the floor (i.e. a brick at 3 meter distance from the chair) returning and sitting down again. Subjects are allowed to use the arms to get up from the chair. The test has to be performed only once. Older patients, who need longer than 10 s to complete the TUG, have an increasingly higher risk of falls [26, 27] and non-vertebral fractures [28]. In the chair rising test (CRT) for testing hip muscle power [29, 30], an individual is requested to stand up and sit down 5 times from a chair of usual height—as quickly as possible—without using the arms. Arms are crossed in front of the chest. Only one test has to be performed. An individual who is not able to sit and rise 5 times or needs more than 10 s to perform the test is at increased risk of fall.

In the tandem gait test (TGT), the patient, starting from a tandem position of both feet, has to perform 8 steps placing one foot in front of the other, toe tips not touching

the heel (a maximal distance of 1 cm between the feet is acceptable) [31]. A step has to be regarded as failure if the foot deviates more than footwide from the line. The best of three attempts is counted.

Statistical analysis

Continuous variables were described with a number of observations that could be evaluated, mean, standard deviation, median, quartiles, 5 and 95% percentiles, minimum and maximum. Descriptive statistics were also calculated for absolute changes from baseline to the last available post-baseline value hereafter named "end of observation".

Categorical variables were displayed by absolute and relative frequencies (percentages). Percentages for categorical variables refer to the number of non-missing values.

AE/ADR was analyzed on a patient and not an event basis, i.e. the number and percentage of patients with at least one event are given.

In addition, statistical tests were performed for the timed up and go test (TUG), chair rising test (CRT) and tandem gait test (TGT). For continuous data, the *t*-test was applied, and for categorical data (percentage of patients with $\leq$10 s for the TUG, CRT and TGT respectively) the chi-square test was used. Two-sided *P*-values were presented with four decimals. All statistical tests were not adjusted for multiplicity; the tests are to be interpreted in an exploratory sense.

Results

Study duration and availability of patients

The mean study duration was 31 weeks (7.15 months). Alfacalcidol therapy was discontinued in 187 of the 2097 patients (9%). A total of 163 discontinued for unknown reasons, 37 were lost to follow-up, and 8 stopped due to adverse events.

Demographic data and risk factors

The mean age of the 2097 patients (women 87.1% and men 12.9%) was 74.8 years, 26.5% were younger than 70 years, 44.6% were between 70 and 80 and 28.5% were older than 80 years. The average body height was of 163.6 cm and body weight of 70.6 kg, i.e. a mean BMI of 26.3 kg/m^2.

A total of 75.3% had a diagnosis of post-menopausal osteoporosis, 13.5% of glucocorticoid-induced osteoporosis and 81% an "increased risk of falls". Among the latter, 72.3% had fallen more than once in the past year. A total of 17% had the clinical diagnosis of impaired renal function, and 70.1% a creatinine clearance lower than 65 ml/min.

Other concomitant diseases were hypertension in 68%, cardiac insufficiency 29%, diabetes 28%, depression 20%, muscle atrophy 14%, dementia 12%, previous stroke 9%, Parkinson's disease 4% and other diagnoses 32%.

Previous and concomitant medication

A total of 64.6% had been prescribed multiple medications (more than 4), and 27.9% used sedatives and/or hypnotics. In 80.7% of the total initial population, at least one previous or concomitant medication was documented. Previous anti-osteoporotic drugs comprised alendronate 38% of patients, other bisphosphonates 9%, calcium 50%, plain vitamin D 14%, calcitriol 3%, raloxifene 2%, strontium ranelate 4%, estrogen 3%, teriparatide 1% and others 26%.

Performance in the different muscle function, muscle power and balance tests

Alfacalcidol therapy was associated with a significantly improved performance in the two muscle tests (TUG and CRT) ($P < 0.001$ in both tests) already after 3 months. This effect ($n = 1970$ for TUG and $n = 1857$ for CRT) further increased between month 3 and the end of trial value (Table 1).

There was a significant increase in the number of participants able to successfully perform the different tests: TUG 24.6% at baseline and 46.3% at the end of trial ($P < 0.0001$) and CRT 21.7 and 44.2%, respectively, ($P < 0.0001$). Thereby, the mean time used for the TUG decreased by 3.0 s (17.0 s at the onset) and by 3.1 s (16.5 s at the onset) for the CRT (Fig. 1). The percentage of patients ($n = 1933$) able to perform the balance test (8 steps in the TGT) increased from 36.0% at onset to 58.6% at the end of the trial ($P < 0.0001$) (Fig. 2).

The percentage of patients who successfully performed the TUG, CRT and TGT tests at the beginning was negatively correlated with age. The younger the patients (<70 years), the higher was the success in performing the tests. At the end of the treatment, the percentage of patients

Table 1 Significant increase in the percentages of patients with successful test performance after alfacalcidol therapy

Treatment time	Successful performance in % of participants		
	TUG $\leq$ 10 s (%)	CRT $\leq$ 10 s (%)	TGT $\geq$ 8 steps (%)
Baseline*	24.6	21.7	36.0
3 months*	35.7	34.3	–
Last value	46.3	44.2	58.6

* In percent of participants

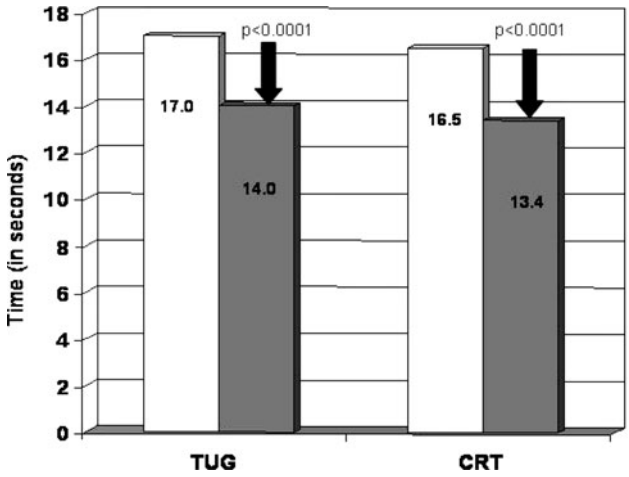

Fig. 1 The average time (in seconds) used for the performance of the "timed up and go" (*TUG*) and "chair rising test" (*CRT*) at the beginning *open square* and end *filled square* of the observation

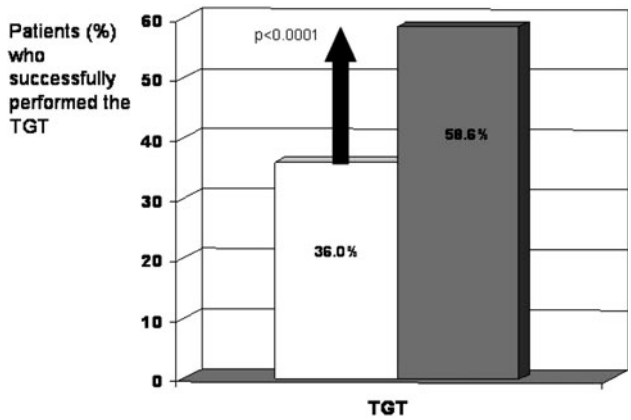

Fig. 2 The percentage of patients (%) who successfully performed the "tandem gait test" (*TGT*) with ≥8 steps at the beginning *open square* and end *filled square* of the observation

in all age groups who successfully performed the studies increased significantly (Fig. 3). However, the older the patients, the lower was the absolute improvement and the higher the relative improvement in the age subgroups.

Timed up and go test (TUG)

The performance results of TUG revealed no dependency on gender. Mean value at baseline decreased significantly by 3.0 s (17.0 s at the onset) during the study observation period (Fig. 3). However, the mean values at baseline differed according to age: patients younger than 70 years needed 13.5 s, patients between 70 and 80 years of age 17.0 s and patients older than 80 years 20.2 s. Also, improvements were different across age groups. Differences were −2.8 s on average for patients younger than 70, −3.2 s for patients between 70 and 80 and −2.7 s for patients older than 80 years.

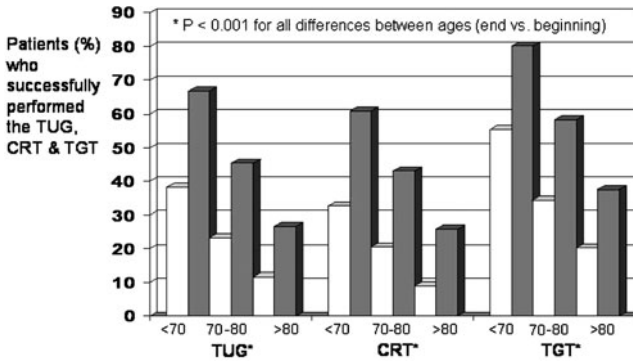

Fig. 3 The percentage of patients (%) who successfully performed the "timed up and go test" (*TUG*), "chair rising test" (*CRT*) and "tandem gait test" (*TGT*) according to their ages: <70 years, 70–80 years, >80 years at the beginning *open square* and end *filled square* of the observation

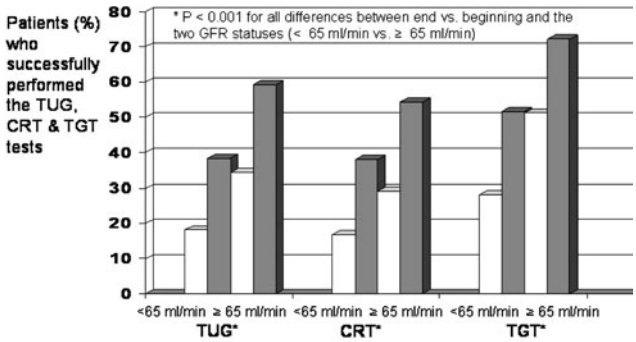

Fig. 4 The percentage of patients (%) who successfully performed the "timed up and go test" (*TUG*), "chair rising test" (*CRT*) and "tandem gait test" (*TGT*) according to their GFR status (<65 ml/min; ≥65 ml/min) at the beginning *open square* and end *filled square* of the observation

In patients with creatinine clearance <65 ml/min, more time was required for TUG with 18.3 s at baseline and a slightly higher improvement was reached (3.3 s) than those with creatinine clearance ≥65 ml/min (baseline value 14.6 s, improvement 2.6 s). Figure 4 shows accordingly in patients with a creatinine clearance below 65 ml/min, lower initial percentages of patients who successfully performed the TUG, CRT and TGT tests and stronger improvements during treatment with the active D-analog than in those patients with a better renal function.

Chair rising test (CRT)

The changes in the ability to perform the CRT showed no dependency on gender and BMI but on age and creatinine clearance. While at baseline, the average time for the total performance time for the entire patient group was 16.5 s, patients younger than 70 years needed 14.3 s, patients between 70 and 80 years of age 16.6 s and patients older than 80 years 19.1 s to perform CRT. Improvements

however were not different across these age groups with 3.1, 3.2 and 3.1 s on average for the respective three age groups. The average reduction for the whole group was significant at 3.1 s (Fig. 1).

Patients with creatinine clearance <65 ml/min had higher baseline values (mean 17.6 s) and a somewhat higher improvement (−3.5 s) than those with creatinine clearance ≥65 ml/min (baseline 14.8 s, difference −2.8 s).

The tandem gait test (TGT)

During the course of observation, the percentage of patients who successfully performed 8 steps of tandem walking increased from 36.0 to 58.6% (Table 1). The absolute increase was 22.6% for TGT and showed no dependency on gender but again on age (Fig. 3). Again, there was an influence of renal function. The subgroup with impaired renal function successfully performing the TGT was before intervention 28.1% and at the end of the trial 51.7%, while the respective values for patients with no impaired kidney function were 51.2 and 72.2% (Fig. 4).

Fear of falls

Fear of falls was significantly reduced by the end of the observation period compared to the beginning (Fig. 5). The fear of falls could be reduced in 74.4% of the 1473 patients with available data from onset to the end of the study. The fear status did not change in 22.6% of the patients ($n = 448$) and deteriorated in 2.9% ($n = 58$). The limitation in household activities was reduced by one point of the five-point score in 60% of the patients ($n = 1185$), no change in 35.6% ($n = 704$) and a deterioration in 4.4% ($n = 86$). Comparable results were obtained for limitations in outdoor activities.

Physical activities and physicians' efficacy assessment

At the beginning, the percentage of patients who performed specific muscle and balance training was 40.1%. During the observation time, this number increased from 40.1 to 60.5% at the end of the observation period. At the end of the study, the investigating physicians assessed the overall efficacy of alfacalcidol therapy in 33.0% as "very good", in 51.0% as "good" and only in 3% as "insufficient".

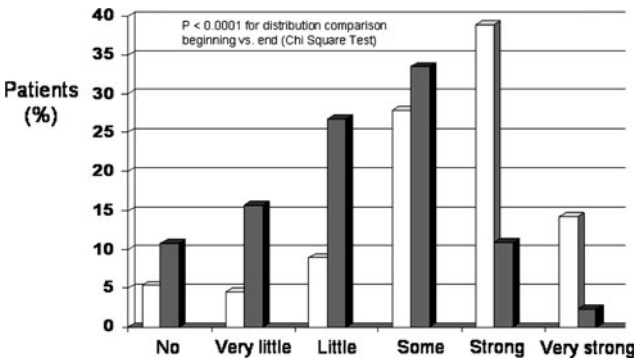

Fig. 5 Patients grading their level of fear of falls at the beginning *open square* and end *filled square* of the observation

Adverse drug reactions (ADR)

Throughout the study, there were 26 adverse drug reactions in 11 out of a total of 2097 patients (incidence 0.52%). No serious adverse drug reactions were documented. A total of 10 of the 26 non-serious adverse drug reactions were classified as "expected" and 16 as "unexpected" according to the current SmPC. Among the latter included 5 incidences of nausea and one incidence each of epigastric pain, agitation, asthenia, chest discomfort, dehydration, gastric disorders, gastroenteritis, general physical health deterioration, hyperhidrosis, malaise, muscle spasm, pruritus, stomach discomfort, vertigo and vomiting.

Discussion

An intact "musculoskeletal system" is the prerequisite for maintaining independence with advancing age. Bones continuously adapt to their function steered by the muscle [4]. The deterioration of muscle power, function and balance is the primary reasons for the increased risk of falls, bone loss and, consequently, the development of osteoporosis and fractures in elderly patients [1, 32, 33].

In order to reduce the fatal sequelae of osteoporotic fractures like loss of independence, social isolation, increased morbidity, mortality and decreased quality of life, specific interventions are indicated. These interventions should aim at both muscle and bone by increasing muscle power and function together with preservation of bone mass, trabecular connectivity and cortical thickness. We chose alfacalcidol, the pro-drug of the active D-hormone calcitriol, because, compared to plain vitamin D, it is independent of the renal 1α-hydroxylase by bypassing the activation in the kidney. It is also effective that in patients with a vitamin D resistance, vitamin D receptor (VDR) status decreased [10], and compared to calcitriol, it is associated with a lower risk of hypercalcemia [34].

To identify elderly persons with a high risk of inability, measurements and questionnaires must be used with high sensitivity in order to characterize these risks. Individual ability to repeat specific physical activities in a defined time must be determined. Previous falling may affect BMD through increased immobility due to self-restriction of physical activities [35]. Falls may lead to psychological trauma known as fear of falls [36]. Successful performance in the chosen tests (TUG ≤ 10 s, CRT ≤ 10 s, TGT ≥ 8

steps) and improvement in the fear of falling and limitations in household and outdoor activities should prove whether alfacalcidol therapy was effective in this real-world trial done by practitioners. Increased muscle capacity and reduced fear of future falls will reduce risk of falls, bone loss and trabecular structure deterioration. Consequently, the risk of fractures, especially hip fractures, should be reduced.

In this prospective, open, uncontrolled study, we found that treatment with 1 μg alfacalcidol daily in elderly patients with reduced bone mass significantly increases their muscle power, muscle function and balance and decreases their fear of falls. After 3 months of treatment with alfacalcidol, participants already showed a statistically significant better performance in the two muscle tests TUG and CRT. This effect was further increased by the end of the therapeutic intervention. There was a significant increase in the number of patients able to successfully perform the different tests (Table 1). The relative increase was higher in the TUG and CRT tests compared to the TGT test. At the end of the trial, the mean time needed for the TUG was decreased by 3.0 s and for the CRT by 3.1 s (Fig. 1). In this context, it is of great interest that a recently published 10-year longitudinal study showed that a mean increase of 2.6 s in the performance of TUG results in a 24% increased risk of non-vertebral fractures [28]. At the end of the observation time, the percentage of participants able to perform the balance test (8 steps in the TGT) increased significantly by 22.6%. All tests showed no gender dependency, and patients' BMI had almost no influence on the outcome of the three tests. Further analysis of the TUG, CRT and TGT results showed age-dependent differences. Elderly patients needed more time to perform the muscle function and power tests at the onset, but the improvement in seconds during the treatment was, interestingly, not different. Looking at the cohort of patients who successfully finished the TUG and CRT, one could say that the older the patients, the lower the absolute improvement and the higher the relative improvement. The percentage of patients able to perform the TGT test at the beginning also decreased with age and again the older the patient, the lower the absolute improvement and the higher the relative improvement in the different age classes. That means alfacalcidol works independently in all age classes, but the better relative improvement in the older age groups found in this study was remarkable.

All tests were obviously dependent on creatinine clearance and renal function. Patients with a CrCl < 65 ml/min had higher baseline values and higher improvement rates than those with a CrCl ≥ 65 ml/min. A low CrCl or impaired renal function is associated with lower calcium absorption, lower availability of D-hormone in the target tissues, lower physical performance, increased risk of osteopenia and osteoporosis, falls and fractures and possibly increased frailty [15–20, 37–39]. The efficacy of alfacalcidol and calcitriol in reducing falls is especially pronounced in patients with low CrCl [17, 40].

As new and very important outcome parameters, we used for the first time the fear of falls and associated limitations in daily life activities. The significant improvements achieved during the study may be explained by the increase in patient awareness as they performed the tests and filled out questionnaires, and the positive feedback of improving test results might have been motivating. The patients understood the importance of self-confidence and taking care to reduce falls. Another factor for the improvement is the pleiotropic effect of the treatment with alfacalcidol [11], including improving muscle function, power and balance as shown in this study as well as possible effects on pain reduction [42, 43], immune system [41, 46] and brain function [48].

We suggest that the highly significant improvements in these parameters during alfacalcidol intake further contribute to a reduction in the risk of falls and non-vertebral fractures [35, 36].

Calcitriol is important if not essential for muscle strength [12, 13], and it has been shown in several studies that a therapy with alfacalcidol or calcitriol significantly improves muscle power and balance [11, 41] and significantly reduces the number of falls and fall-associated fractures in older persons [7, 8, 17, 40]. Higher D-hormone serum concentrations in the elderly are significantly associated with increased leg extension power [44] and better muscle function [45]. The cross-sectional area and number of fast-twitch (type IIA) muscle fibers have been shown to increase within 3 months under a treatment with alfacalcidol 1 mcg per day in osteoporotic older women [46]. The substitution of the active D-hormone analog improves muscle strength (isometric knee extension strength) and functional ability (walking distance over 2 min) significantly after 6 months of treatment in elderly D-hormone-deficient women [47]. Patients with rheumatoid arthritis, osteopenia and normal vitamin D levels who received a daily dose of 1 mcg of alfacalcidol showed a significant increase in muscle power (60%) compared to only an 18% increase in those patients who received a daily dose of 1000 IU of plain vitamin D [43].

In a recent study of glucocorticoid-treated rats, alfacalcidol prevented not only a decrease in the BMD, but also muscle atrophy [48]. Gallagher showed in the STOPIT study that physical performance, tested with the chair rising or timed walking test, declines with age [8] and that a treatment with 0.5 mcg D-hormone daily over 3 years could delay the decline of physical performance in this population. In a cross-sectional study, it was suggested that long-term treatment with alfacalcidol could improve body

sway, e.g. improve balance disorders in elderly women [49]. In the above-mentioned prospective, randomized, placebo-controlled trial of 3 years (STOPIT study), it was shown that daily treatment with 0.5 mcg calcitriol significantly reduced the rate of falls by 38% in older osteopenic, vitamin-D-replete women [8], and in another prospective, randomized, placebo-controlled trial of 36 weeks, treatment with 1 mcg alfacalcidol daily was associated with a significant 55% reduction in number of fallers and a significantly reduced fall rate by 54% in elderly, vitamin-D-replete men and women with calcium intake above 512 mg daily [7].

A comparative meta-analysis to clarify the open question of differentiation of the efficacy of plain vitamin D in comparison to D-hormone analogs on falls was performed by Richy et al. [9]. Based on randomized, double-blind controlled clinical studies, the reduction in the absolute risk of falls was 3.5 times higher with D-hormone analogs (alfacalcidol, calcitriol) than with plain vitamin D, and the number needed to treat to avoid one fall was 12 vs. 52 D-hormone analogs provided a statistically significant lower level of risk of falling compared to plain vitamin D: RR = 0.79 (95% CI 0.64–0.96) vs. RR = 0.94 (95% CI 0.87–1.01) (inter-group difference $P = 0.049$). The respective efficacies of alfacalcidol and native vitamin D on BMD, falls and fractures were also described in two very recent reviews [50, 51].

Impaired renal function observed with aging leads to decreased activity of the renal 1α-hydroxylase and consecutively to low D-Hormone serum levels. Faulkner et al. showed that only higher D-hormone concentrations are significantly associated with lower risk of falls in older community-dwelling women, whereas vitamin D supplementation and calcidiol and PTH concentrations were not associated with either neuromuscular function or falls [52].

Based on the results of this study as well as from numerous others [11–13, 15, 18, 19, 37, 38, 44, 51], we suggest that calcitriol is directly involved in the pathogenetic cascade of decreased muscle strength, decreased balance, related falls and fractures and that treatment with the calcitriol analog alfacalcidol significantly improves muscle power, muscle function and balance and reduces significantly the number of falls and fallers, fall-related fractures and fear of falls [7–9, 17, 40, 53–58].

There are important limitations in this study. Since this is an open, uncontrolled, prospective study, the interpretation of our study results should be done with caution. A "study effect" by learning to improve the test performances cannot be excluded. Based on the fact that there was an increase in physical activity only by approximately 20% from 40.1 to 60.5%, we conclude that the "study effect" can only partially explain the good results. In general, we could also not control for other important covariates such as co-morbidity, number of medications and other non-assessed variables. Finally, the diagnosis of osteoporosis in the Caucasian elderly men and women was based on different radiological methods. Accordingly, our findings cannot be generalized for a mixed osteoporotic population, a younger population, or to osteoporotic men and women of other races.

Conclusion and outlook

We conclude that treatment with 1 mcg daily of alfacalcidol is safe, increases muscle power, muscle function and balance and decreases fear of falls. The significant improvement in the fall risk tests timed up and go test (TUG), chair rising test (CRT) and tandem gait test (TGT) after 3 as well as 6 months of treatment with alfacalcidol 1 mcg daily should definitely have an effect on falls and thereby fracture risk, especially on fall-related fractures such as hip fractures. It is well known that hip fractures are the most important risk factor for the transfer from frailty to disability. Fear of falling results in self-restriction from physical activities and reduction in social contacts. The significant reduction in this fear and the increase in daily activities during alfacalcidol treatment in the majority of the patients should increase the quality of life.

The described simple measurements and questionnaires used in our study open up additional, quantitative possibilities for assessing the risk of falls and hip fractures. The adopted tests to measure and document the effects of alfacalcidol were validated as useful in this trial, and the positive results are appropriate to motivate the patients to continue the pharmacological and physical treatments. The fact that it has been shown in a 10-year longitudinal study that the TUG test is not only a measurement of functional mobility, but also a confirmed predictor for non-vertebral fall-related fractures is of great value. The chance for the delay of frailty and the prevention of disability, both strongly correlated with muscle weakness and hip fractures, is of great social and economic relevance. There is an urgent need to confirm our results by double-blind clinical studies.

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