# ORIGINAL ARTICLE

# Treatment with alfacalcidol in elderly people significantly decreases the high risk of falls associated with a low creatinine clearance of <65 ml/min

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Abstract We previously observed that a creatinine clearance (CrCl) of <65 ml/min is a significant and independent risk factor for the number of fallers and falls in a community-dwelling elderly population and postulated that this increased risk is due to the associated significant lower D-hormone serum levels. To test our hypothesis, we investigated in a post hoc analysis of a double-blind randomized study whether treatment with alfacalcidol, a synthetic prodrug of the D-hormone, can reduce the high incidence of fallers and the high risk of falls associated with low CrCl. Of 378 Swiss community-dwelling women (n=191) and men (n=187), aged 70 years and older, 191 received randomly 1 µg capsules of alfacalcidol (AlphaD3: Teva), and 187 received one capsule of placebo daily. With the help of questionnaires we regularly assessed the incidence and frequency of falls. The risk of becoming a faller and the risk of falling were assessed in multivariate-controlled logistic regression models according to treatment groups and according to a CrCl cut-off of 65 ml/min. The presented results are from ITT analyses. In participants with a CrCl of < 65 ml/min, the 36 weeks of treatment with alfacalcidol was, compared

with placebo, associated with a significant reduction in the number of fallers (14/72 versus 25/70; OR 0.26, 95% CI 0.08–0.80, P = 0.019), and a significant reduction of the number of falls (16/72 versus 28/70; OR 0.29, 95% CI 0.09–0.88, P = 0.028). No such association was observed in participants with a CrCl of ≥65 ml/min (for fallers 26/120 versus 21/116; OR 0.92 95% CI 0.34-2.52, P = 0.875; for falls 32/120 versus 23/116; OR 0.93 95% CI 0.34–2.54, P = 0.885). In the placebo group frequency of falls was dependent on CrCl (P = 0.006), whereas in the alfacalcidol treatment group frequency of falls was independent of CrCl (P = 0.494). No cases of clinically relevant hypercalcemia were observed. In a community-dwelling population of elderly men and women with a CrCl of <65 ml/min, treatment with alfacalcidol can significantly and safely reduce the low CrCl associated increased number of fallers and the high risk of falls.

**Keywords** Alfacalcidol · Creatinine clearance · Elderly · Fallers · Falls

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## Introduction

Recently published studies [1, 2] have shown that treatment with either calcitriol in osteopenic vitamin D replete women [1] or alfacacidiol, a synthetic D-hormone pro-drug, in a population of community-dwelling elderly vitamin D replete men and women [2] can significantly reduce the frequency of falls [1, 2] and number of fallers [2]. This positive effect of calcitriol or alfacalcidol on risk of falls or number of fallers is most probably due to an increase in muscle strength [3, 4, 5] and neuromuscular coordination [6], improved balance [4, 5, 7] and increased functional mobility [5, 8] observed with increasing D-hormone serum levels or under treatment with calcitriol or alfacalcidol [7, 9].

We found that a creatinine clearance of <65 ml/min is a significant independent new risk factor for an

increased frequency of falls and for becoming a faller in a community-dwelling elderly population of men and women. The reduced serum creatinine clearance of < 65 ml/min was significantly associated with low D-hormone serum concentrations, and low D-hormone serum levels have been associated with an increased risk of falls or risk of becoming a faller [9, 10, 11, 12]. We therefore postulated that the low CrCl associated risk of falls and risk of becoming a faller, which we observed in vitamin D replete elderly men and women, is due to the low CrCl associated low D-hormone serum levels. Therefore, we investigated in a post-hoc analysis in this same population of community-dwelling elderly men and women, if treatment with alfacalcidol could reduce the low creatinine clearance associated risk of falls and risk of becoming a faller.

## **Materials and methods**

This investigation was conducted as a post-hoc analysis of the Swiss Aims Study [2]. The Aims study was a large double-blind placebo-controlled randomized study to assess the influence of a 36-week treatment with alfacalcidol (1α-dihydroxycholcalcitriol, AlphaD<sub>3</sub>; Teva Pharmaceutical Industries, Jerusalem, Israel), a D-hormone pro-drug, on frequency of fallers and falls in community-dwelling elderly men and women, 70 years old and older. The study has previously been described in detail [2]. Of the 378 participants (191 women and 187 men), aged 70 years old and older, 191 randomly received 1 µg capsules of alfacalcidol, and 187 received one capsule of placebo daily. Falls were assessed every 12 weeks after the baseline visit for a total of 36 weeks. The procedure for assessment of falls has been previously described in detail [2]. The dietary calcium and vitamin D intake was estimated by using a modified food frequency questionnaire [13], which also gave information on some demographic, lifestyle and nutritional parameters. Calcium was not supplied, none of the participants was receiving physical therapy or training programs at study entry, and no attempt was made to alter subjects' diet or physical activity during the study. In all subjects, blood samples were drawn for measurement of serum calcium, phosphate, creatinine, calcidiol, D-hormone and iPTH. Calcidiol, D-hormone and iPTH serum levels were measured by radioimmunoassay (Nichols). In this manuscript, we use the terminology of D-hormone for 1,25-dihydroxycalcitriol to clearly differentiate between vitamin D and the hormonal activity of D-hormone. The protocol of this study was approved by the Ethical Review Board of the University of Basel, and all participants provided written informed consent. The Data, Safety and Monitoring Board established by GWD Consult Germany (Safety and Monitoring Board: GWD Consult, Research Contract, Postfach 1210, 63152 Mülheim/Main, Germany), reviewed the conduct of the study.

## Statistical analyses

Comparisons of means were performed by multivariate adjusted analyses of variance [14]. The main follow-up multivariate analysis compared the number of fallers and falls in the two treatment groups according to a previously determined cut-off value for creatinine clearance set at 65 ml/min. Those factors that reached significance level of P < 0.1 in a screening regression model were entered into a logistic regression model. Multivariate difference in number of fallers and falls between treatment groups are given as odds ratio (OR) with 95% confidence intervals (CI). According to our previously published results [2] on the effect of total daily calcium intake on the treatment with alfacalcidol, we also performed subgroup analyses according to creatinine clearance and total daily calcium intake; even so, our study was not designed and did not have the power to detect significant differences in such small subgroups. The results presented are from multivariate-controlled ITT analyses. A 5% significance level was maintained throughout these analyses, and all tests were two-sided.

The statistical analyses were conducted using the SAS statistical software package, version 8.2, by the SAS Institute Inc., Cary N.C., USA, licensed to the University of Basel, Switzerland.

### Results

General

The two treatment groups were comparable at baseline. A significant difference was found only for the use of phenprocoumon. Average dietary calcium intake was generally low [mean( $\pm$ SD) daily intake in mg:  $512 \pm 197$ , respectively  $521 \pm 147$ ]. The proportion of men to women was the same in each treatment group and major comorbid conditions were equally distributed between treatment groups (data not shown). Also, in participants with a creatinine clearance of ≥65 ml/min, the two treatment groups were comparable at baseline, with a comparable gender distribution. A significant difference was found only for the use of aspirin, and average dietary calcium intake was also generally low (mean  $\pm$  SD daily intake in mg:  $530 \pm 167$ , respectively  $514 \pm 159$ ). Comorbid conditions were equally distributed between treatment groups (data not shown).

Compared with participants with a creatinine clearance of  $\geq 65$  ml/min, participants with a creatinine clearance of < 65 ml/min were multivariate controlled significantly older (P < 0.0001), and had multivariate controlled significant lower BMI (P < 0.0001), lower D-hormone serum levels (P = 0.010) and lower bone density measured as T-score with ultrasound of the calcaneus (P = 0.023). Furthermore, participants with a creatinine clearance of < 65 ml/min were significantly more likely to be female (P = 0.030) and to live alone (P = 0.042), were less likely to be diabetic (P = 0.048),

were significantly more likely to be under a daily medication with digoxin (P = 0.032), diuretics (P = 0.005) and alternative medicine (P = 0.018) and were less physically active (P = 0.015) (Table 1). For all other variables we found no significant differences between groups according to creatinine clearance.

# Follow-up

Of the 378 participants enrolled, 321 [84.3% / 158 women (82.7%) and 163 men (87.2%)] completed the study, with no difference in completion rate between treatment groups (placebo 83.3% versus alfacalcidol 86.5%, P=0.649) During the study there were two deaths, both in the group with a CrCl < 65 ml/min: one man on placebo, with long-standing heart disease, died from myocardial infarction, and one man on alfacalcidol after a bout of influenza died from pneumonia and

subsequent hepatitis (P = 0.982, for the difference in death rates according to treatment group).

Fallers and falls (Table 2, Fig. 1 and 2)

The multivariate analyses included predictors which have been previously shown to be associated with increased risk of falling, or variables which were significantly different between treatment groups. These variables were: age, gender, body mass index (BMI), creatinine clearance (ml/min), number of falls in previous 3 months, physical activity (sport yes/no), Charlson comorbidity index, number of medications at baseline, dietary calcium intake, heart rate at baseline (<80 beats/min versus ≥80 beats/min), D-hormone (pg/ml), calcidiol (ng/ml), iPTH (pg/ml), creatinine (μmol/l) and albumin (g/l) serum levels at baseline, changes in D-hormone, calcidiol and iPTH serum levels over time

Table 1 Comparison of the

Categories	CrCl < 65 ml/min (n = 142)	CrCl ≥65 ml/min (n = 236)	<i>P</i> -value
Gender (number), male/female Age (mean ± SD) years	60/82 76.6 ± 4.5	127/109 74.0 ± 3.8	0.030 < 0.0001
BMI (mean $\pm$ SD) kg/m <sup>2</sup>	$24.6 \pm 3.0$	$27.5 \pm 3.9$	< 0.0001
Laboratory $(mean \pm SD)$			
iPTH pg/ml	$40.6 \pm 27.5$	$36.4 \pm 15.4$	0.057
D-hormone pg/ml	$37.6 \pm 11.9$	$40.7 \pm 11.2$	0.010
Calcidiol ng/ml	$28.5 \pm 11.8$	$29.8 \pm 15.8$	0.422
Albumin g/l	$42.5 \pm 2.8$	$42.1 \pm 2.9$	0.150
Drug intake (in %)			
Use of alternative medicine	7.2%	2.1%	0.018
Use of digoxin	4.9%	1.3%	0.032
Use of diuretics	23.3%	17.8%	0.005
Other variables (in % or mean $\pm SD$ )			
Living alone	38.0%	28.0%	0.042
Number of diabetics	1.4%	5.5%	0.048
History of falls in previous 3 months before study entry	12.7%	10.7%	0.453
Regular physical activity (yes)	33.1%	45.7%	0.015
Daily dietary calcium intake (mg)	$516 \pm 172$	$522\pm163$	0.751
Bone density QUS ( <i>T</i> -score)	$-1.08 \pm 1.58$	$-0.64 \pm 1.39$	0.023
Timed up and go test (s)	$7.0 \pm 1.8$	$6.9 \pm 1.7$	0.518

characteristics of the study participants with a Creatinine clearance of <65 ml/min vs ≥65 ml/min. *BMI* body mass index, *iPTH* intact parathormone, *QUS* quantitative ultrasound (calcaneus), controlled for gender

**Table 2** Effect of alfacalcidol in elderly men and women on number of fallers and falls according to creatinine clearance: cut-off < 65 ml/min ≥65 ml/min

Creatinine clearance	Parameter	Multivariate Adjusted OR (95% CI)	Number of fallers/falls Alfacalcidol vs Placebo	P-value
< 65 ml/min Fallers Falls	Fallers	0.26 (0.08–0.80)	14/25	0.019 <sup>a</sup>
	Falls	0.29 (0.09–0.88)	16/28	$0.028^{a}$
≥65 ml/min Fallers Falls	Fallers	0.92 (0.34–2.52)	26/21	$0.875^{a}$
	Falls	0.93 (0.34–2.54)	32/23	$0.885^{a}$

<sup>&</sup>lt;sup>a</sup>Controlled for age, gender, BMI, previous falls, use of diuretics, albumin serum levels, calcidiol, D-hormone and iPTH serum levels at baseline and during follow-up, total daily calcium intake and coffee consumption, use of diuretics, marcoumar, aspirin, estrogens and multivitamins, number of co-morbidities and physical activity

**Fig. 1** Number of fallers over time according to treatment groups

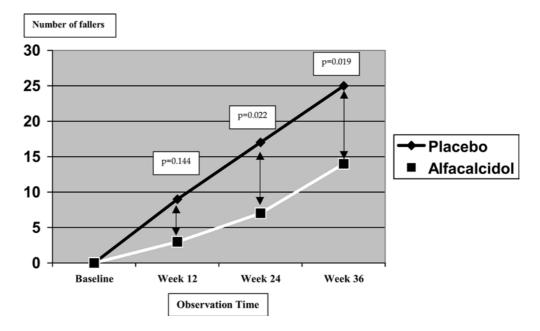
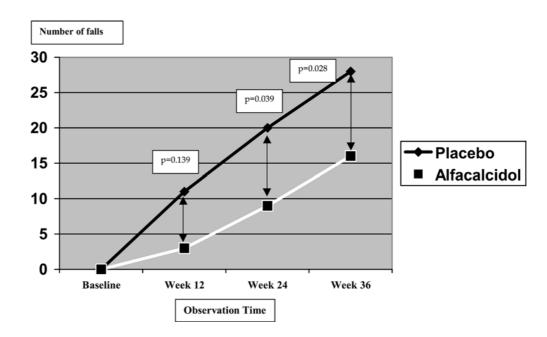


Fig. 2 Number of falls over time according to treatment groups



in percent, coffee intake, use of estrogen, phenprocoumon and aspirin.

In the multivariate adjusted logistic regression analyses, treatment with alfacalcidol over 36 weeks was, compared with placebo, in participants with a creatinine clearance below 65 ml/min associated with a significant reduction in number of fallers (14/72 versus 25/70; OR 0.26, 95% CI 0.08–0.80, P=0.019), and a significant reduction in the number of falls (16/72 versus 28/70; OR 0.29, 95% CI 0.09–0.88, P=0.028) (Table 2). No such association was observed in participants with a CrCl of  $\geq$ 65 ml/min (for fallers 26/120 versus 21/116; OR 0.92 95% CI 0.34–2.52, P=0.875; for falls 32/120 versus 23/116; OR 0.93 95% CI 0.34–2.54, P=0.885) (Table 2).

The difference in the reduction of number of fallers and number of falls between treatment groups became already significant after 24 weeks of intervention for number of fallers and for number of falls (alfacalcidol versus placebo week 24: number of fallers 7 versus 17, OR 0.18 95% CI 0.014–0.078, P = 0.022; number of falls 9 versus 20, OR 0.22 95% CI 0.05–0.93, P = 0.039) (Fig. 1 and 2).

In subgroup analyses of participants with creatinine clearance of <65 ml/min according to the median of total daily calcium intake, alfacalcidol had a non-significant greater effect in participants who were stratified in the group above the median of total daily calcium intake compared with participants stratified into the

group below the median daily of total daily calcium intake (OR 0.30 95% CI 0.07–1.25 versus OR 0.66 95% CI 0.18–2.38) (data not shown). In the alfacalcidol treatment group, frequency of falls was independent from CrCl (P = 0.494) (data not shown).

#### Adverse events and side effects

During the 36 weeks of intervention, we observed six cases [one case in the placebo (CrCl ≥65 ml/min) group and five cases in the alfacalcidol group (one with a CrCl ≥65 ml/min and four with a CrCl <65 ml/min)] of slight transient hypercalcemia (one measurement of serum calcium above normal with subsequent (1 week later) control measurement within normal ranges), the highest value measured being 2.73 mmol/l (normal range 2.10-2.65 mmol/l). This slight transient increase in serum calcium did not lead to a modification of the dose of alfacalcidol. Two participants in the alfacalcidol group, one with a CrCl ≥65 ml/min and one with a CrCl < 65 ml/min), presented after 12 weeks of intervention continuously till the end of the study elevated calcium serum levels (highest value 3.00 mmol/l), without clinical symptoms. One of these participants admitted at the end of the study to having taken supplementary calcium (1000 mg daily). The difference in the incidence of hypercalcemia between study groups and according to CrCl was not significant (P=0.0621, respectively)P = 0.260). Furthermore, we observed no differences in the frequency of major diseases occurring during the 36 weeks between treatment groups and no cases of serious adverse events attributable to alfacalcidol treatment. Frequency of reported side effects was equally distributed between treatment groups (82 cases in placebo versus 75 cases in alfacalcidol, P = 0.850) and independent from creatinine clearance (P = 0.878). The most common side effects were itching (placebo treatment group: 23 cases/alfacalcidol treatment group: 22 cases) and skin eruption (placebo treatment group: 11 cases/ alfacalcidol treatment groups 15 cases).

#### Discussion

We are the first to describe a low creatinine clearance associated risk for falls and risk of becoming a faller, which we attributed to the significantly lower D-hormone serum levels observed with a creatinine clearance below 65 ml/min. Therefore, we are also the first to have studied the effect of treatment with alfacalcidol on low creatinine clearance associated risk of falls. We observed in community-dwelling elderly men and women that treatment with alfacalcidol significantly reduced the high risk of falls and risk of becoming a faller associated with a creatinine clearance < 65 ml/min. The treatment effect of alfacalcidol on number of fallers and number of falls already became significant after 24 weeks of treatment with alfacalcidol. In participants with a CrCl < 65 ml/

min, alfacalcidol reduced the frequency of fallers and falls to the frequency of fallers and falls observed in participants with a CrCl ≥65 ml/min, for whom we found no difference in fall and faller frequency between treatment groups.

D-hormone has a scientifically established effect on muscle strength, balance and functional mobility [3, 4, 5, 6, 7, 8, 9], and the effect of D-hormone treatment (alfacalcidol or calcitriol) on risk of falls has been proven in several studies [1, 2]. The low D-hormone serum levels observed with a creatinine clearance of < 65 ml/min may also be one reason for the increased osteopenia and osteoporosis observed with low creatinine clearance by other authors [15, 16]. Our result enhances the theory suggested by other studies [4, 5, 6, 7, 17, 18, 19, 20, 21, 22] that D-hormone is an independent risk factor for falls [1, 2, 5, 23], and that D-hormone is directly involved in the causal pathogenic pathway of decreased muscle strength related falls [9, 23, 24]. It has been recently confirmed in VDR gene deleted mice that the absence of VDR causes muscle abnormality independently of secondary metabolic changes, e.g. hypocalcemia or hyperparathyroidism, and that treatment with D-hormone counterbalances the abnormalities in myoblastic cells and is necessary for optimal muscle differentiation [25]. We therefore conclude that our previously observed approximately 4 times increased risk of falls observed in participants with a low creatinine clearance is due to a creatinine clearance dependent decrease in D-hormone serum levels. Therefore treatment options for patients at risk for falls should clearly differentiate between nutritive vitamin D deficiency and metabolic low D-hormone syndrome [18, 19, 20, 21].

We found an increased treatment effect of alfacalcidol on frequency of fallers and falls in participants with a CrCl < 65 ml/min and a total daily calcium intake above the median of 512 mg compared with participants with a CrCl < 65 ml/min and daily total calcium intake below 512 mg. The influence of calcium intake on the treatment effect of alfacalcidol on frequency of falls and fallers was described by us previously [2]; however, in participants with a CrCl < 65 ml/min, the influence of calcium intake on the treatment effect of alfacalcidol was not significant. This result may be due to the fact that our study was not designed for power analyses in small subgroups.

Our study has several limitations. The results come from post hoc analyses. The participants were Caucasian community-dwelling men and women over the age of 70 years, so our findings are not generalizable to a younger population, institutionalized elderly or to men and women of other races. Since our analyses were performed in participants who received placebo during 36 weeks, we cannot rule out an influence in either direction of placebo on risk of falls. Assessment of risk factors for falls as well as the large majority of incidence of falls during the study was based only on the participant's own report. Finally, we cannot exclude uncontrolled confounding.

In conclusion a low creatinine clearance of < 65 ml/min associated increased risk of becoming a faller and increased risk for falls can significantly be treated with alfacalcidol. Our result confirms our hypothesis that the low creatinine clearance of < 65 ml/min. associated risk of becoming a faller and for falls is due to low creatinine clearance associated low D-hormone.

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