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ORIGINAL ARTICLE

In elderly men and women treated for osteoporosis a low creatinine clearance of <65 ml/min is a risk factor for falls and fractures

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Abstract Recently, a low creatinine clearance (CrCl) of <65 ml/min was described as a new significant and independent risk factor for the number of fallers and falls in a community-dwelling elderly population. In this study we investigated if a low creatinine clearance of <65 ml/min is also a risk factor for falls and fractures in elderly men and women treated for osteoporosis. In a cross-sectional study with the help of questionnaires we assessed the prevalence of having experienced falls within the last 12 months according to renal function in 5,313 German men and women receiving treatment for osteoporosis. The CrCl was calculated using the established Cockcroft-Gault formula. The prevalence of falls and fractures was assessed in multivariate-controlled logistic regression models according to a CrCl cut off of 65 ml/min. The *P* -values were two-sided. In this study of elderly men and women treated for osteoporosis ($n=5,313$), 60.9% ($n=3,238$) had a CrCl of <65 ml/min, which was associated in multivariate controlled analyses, compared to a CrCl of ≥65 ml/min ($n=2,075$), with a significant increased risk of experiencing falls (1,775/3,238 vs. 773/2,075, OR 1.69, 95% CI 1.50–1.91, $P<0.0001$) and an increased risk for multiple falls (37.1 vs. 22.6%, OR 1.63, 95% CI 1.42–1.87, $P<0.0001$). Furthermore, compared to a creatinine clearance of ≥65 ml/min, a creatinine clearance of <65 ml/min was also associated with a significant increased multivariate controlled risk for hip fractures (OR 1.57, 95%CI 1.18–2.09, $P=0.002$), for radial fractures (OR 1.79, 95%CI 1.39–2.31, $P=<0.0001$), for total vertebral fractures (OR 1.31, 95%CI 1.19–1.55, $P=0.003$) and for fall-associated vertebral fractures (OR 1.24, 95% CI 1.03–1.54, $P=0.031$). Similar to community-dwelling elderly, in elderly men and women treated for osteoporosis a CrCl of less than 65 ml/min is a significant and independent risk factor for falls. Furthermore, we could show for the first time that a low creatinine clearance in elderly men and women treated for osteoporosis is also associated with a significantly increased risk of vertebral, hip and radial fractures.

Keywords Creatinine clearance · Osteoporosis treatment · Falls · Fractures

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Introduction

Recently, a low creatinine clearance of <65 ml/min was described as a new and independent risk factor for falls in elderly community-dwelling men and women [1]. It could be shown in another recently published study that the low creatinine clearance associated increased risk of falls, and increased number of fallers can effectively be treated with alfacalcidol, a synthetic D-hormone prodrug [2]. The observed effect of alfacalcidol on the number of falls and fallers observed in participants with a creatinine clearance of <65 ml/min is most probably due to increased D-hormone levels in the serum or at the target organ's muscles and nerves, which have been associated with an increase of muscle strength [3, 4, 5] and neuromuscular coordination [5, 6], improved balance [7] and increased functional mobility [8, 9]. The conversion of calcidiol [$25(OH)D_3$] to the metabolically most active form of vitamin D, the D-hormone [calcitriol; 1, $25(OH)_2$ D_3] is highly dependent on the creatinine clearance [10, 11, 12]. Even a slight decrease in D-hormone and a corresponding slight increase in iPTH

serum levels, observed when creatinine clearance (CrCl) decreases to 60–80 ml/min [13], is associated with subclinical myopathy and balance trouble [3, 4, 14, 15].

It is nowadays accepted that an increased occurrence of falling among men and women suffering from osteoporosis together with increased skeletal fragility has a larger effect on the increased frequency of fractures than bone mass alone [16, 17]. At least 90% of all hip fractures are due to an age-related decline in muscle strength and increased bone fragility, which are both strongly associated with an increase in falls [18]. The currently published updated Kidney Disease Outcomes Quality Initiative practice guidelines by the US Kidney Foundation (K/DOQI) [19] mention that a slight decrease of the CrCl is associated with a decrease in bone mineral density [20], and since a CrCl below 60 ml/min increases the risk of fractures significantly, the guidelines suggest an intensive control of patients with decreased creatinine clearance [19]. A low creatinine clearance associated with increased risk of falls and fallers in osteoporotic men and women, which could easily be treated with D-hormone, would have a tremendous impact on the prevention of osteoporotic fractures. To test our hypothesis that a low creatinine clearance is also a risk factor for falls in osteoporotic patients, we investigated if a low creatinine clearance of < 65 ml/min is associated with an increased risk of falls and risk to become a faller in an elderly population of German men and women treated for osteoporosis.

Subjects and methods

This study is a cross-sectional analysis of a German study that was conducted from May 2002 till March 2003. The aim of this study was to assess the association between osteoporosis and renal function in osteoporotic German women and men aged 65 and older. Therefore GPs, specialists in internal medicine and orthopedists involved in the treatment of osteoporotic patients were asked to fill in a questionnaire concerning their patients treated for osteoporosis. Four hundred fifty-five medical centers from all over Germany participated in this study. The questionnaire had to be filled out in the presence and with the help of the patient treated for osteoporosis at a medical visit during the study time period.

The questionnaire gave information on some demographic and, if available, laboratory parameters as well as parameters of osteoporosis and falls. Demographic parameters included gender, age, weight, height and intake of some specific long-term medication [immunosuppressive therapy (no specification), corticosteroids, anticoagulants (oral/parenteral) and vitamin D and calcium]. Laboratory parameters included serum levels of creatinine, calcium and phosphate. Alkaline phosphatase, calcidiol, calcitriol, and iPTH serum levels as well as C-reactive protein (CRP) were available only for a tiny minority of participants. Creatinine clearance was calculated using the well-established formula from Cockcroft-Gault, adjusted for gender [21]. The Cockcroft-Gault formula is widely accepted and used for the calculation of the creatinine clearance. However, it gives only an estimate of the GFR as compared to a direct measurement of the GFR with 24-h urine sampling or inulin clearance. Parameters of osteoporosis included the exact date of the diagnosis of osteoporosis (DD/MM/YY), the tools used for the diagnosis of osteoporosis (clinical investigation, X-ray, DEXA, ultrasound or laboratory) as well as anti-osteoporotic treatment [biphosphonates (yes/no), fluoride (yes/no), raloxifen (yes/no), alfacalcidol (yes/no) and others (yes/no, with specification, i.e., calcium or vitamin D alone)]. The duration, dosage of anti-osteoporotic treatment and possible switches of therapy were not assessed. The diagnostic criteria for osteoporosis used by the physician were not assessed. Therefore, in this study the diagnosis of osteoporosis was solely based on the physician's report. Assessment of falls and frequency of falls was based on recall of the past 12 months. Parameters for falls and fractures included the number of falls and fractures during the last 12 months, experience of pain (muscle pain/pain in the bone), pain severity (heavy, medium, light), localization of a possible fracture (vertebral, hip, radius, other) and the question if the fracture(s) were associated to osteoporosis. Falls were not defined, and the participating physicians were not trained in the assessment of falls. Fracture incidence within the last 12 months was assessed as documented in the medical history of each individual participant and not based on the patient's recall. 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 study.

The main follow-up multivariate analysis compared the number of fallers and falls in the two groups according to the cutoff value for creatinine clearance set at 65 ml/min. The multivariate difference in the number of fallers and falls between groups is given as odds ratio (OR) with 95% confidence intervals (CI). We also assessed the number of fractures according to the CrCl. For the main analyses we used ANCOVA and pooled linear regression models to control simultaneously for several potentially confounding variables. Comparisons of means were performed by multivariate adjusted analyses of variance [22]. Since age and BMI distributions were markedly skewed, logarithmic transformation of these variables was performed prior to analyses. The multivariate analyses included predictors that have been previously shown to be associated with an increased risk of falling or variables that were significantly different between treatment groups. These covariates were gender (male, female), age and body mass index (BMI). In the main analyses we used only laboratory variables that were available for all participants. These variables were serum levels of creatinine, calcium and phosphate. Age, BMI and creatinine clearance were analyzed as continuous variables as well as categorical variables

[age categories: younger than 65 ($n=149$), 65–69 years ($n=1,513$), 70–74 years ($n=1,383$), 75–79 years ($n=1,099$), 80–84 years ($n=788$), 85 and older ($n=435$)/ BMI categories: <19 kg/m^2 ($n=125$), 19–24 kg/m^2 ($n=2,104$), 25–29 kg/m^2 ($n=2,382$), 30 kg/m^2 and more ($n=756$)]. For all other analyses we used the t -test, Wilcoxon rank sum test and chi-square.

Since according to recently published data [1] a creatinine clearance of <65 ml/min has been found to be significantly associated with decreasing D-hormone serum levels and a significantly increased risk of falls in community-dwelling elderly men and women, we also set the threshold for creatinine clearance at 65 ml/min in this study. 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., licensed to the University of Basel, Switzerland.

Results

General

Participating in this study were 5,481 German men and women treated for osteoporosis. Of them, 168 were deleted from the analyses because of missing values for the main outcome variable (creatinine, res. creatinine clearance) or missing values for gender, age or BMI. From the 5,313 included participants, 1,067 (20.1%) were men and 4,246 (79.9%) were women. The mean age was 74.0 years. Men were significantly younger (mean age: 73.0 ± 6.6 vs. 74.2 ± 7.3 years, $P<0.0001$) and had a significantly higher BMI than women (26.3 ± 3.6 kg/m^2 vs. 25.9 ± 4.0 kg/m^2, $P=0.029$)

Concerning the specific long-term medical treatment assessed in this study, 7.2% ($n=380$) had had long-term immunosuppressive therapy, 23.3% ($n=1,236$) had received long-term therapy with glucocorticoids, 16.5% ($n=875$) were under treatment with anticoagulants and 56.9% ($n=3,025$) had received long-term therapy with vitamin D and calcium. Significantly more women than men in this study group were under these specific long-term therapies (women vs. men: immunosuppressive therapy 5.4 vs. 1.8%, $P=0.026$/corticosteroids: 17.1 vs. 6.2%, $P<0.0001$/anticoagulants: 11.8 vs. 4.7%, $P<0.0001$/vitamin D and calcium: 47.6 vs. 9.3%, $P<0.0001$). Concerning anti-osteoporotic treatment, 31.7% of the participants were treated with biphosphonates, 12.4% with fluorides, 3.9% with raloxifen, 29.3% with alfacalcidol and 3.6% received another treatment. For 19.1% of the participants, we have no specification about the anti-osteoporotic treatment.

Laboratory

The mean creatinine clearance in the participants of this study was 59.4 ± 23.3 ml/min. Men had a significantly higher creatinine clearance than women (men vs. women: 67.2 ± 23.5 vs. 57.5 ± 22.8, $P<0.0001$). Of the participating osteoporotic men and women, 60.9% were found to have creatinine clearance of <65 ml/min (3,328/5,313 vs. 2,075/5,313).

Participants with a creatinine clearance of <65 ml/min as compared to participants with a creatinine clearance of ≥65 ml/min were significantly more prone to be of female gender (women vs. men: 64.4 vs. 35.6%, $P<0.0001$), were significantly older (76.0 ± 6.2 vs. 70.8 ± 7.04 years, $P<0.0001$, controlled for gender) and had a significantly lower BMI (25.1 ± 3.3 kg/m^2 vs. 27.5 ± 4.0 kg/m^2, $P<0.0001$, controlled for gender) (Table 1).

As compared to participants with a creatinine clearance of ≥65 ml/min, participants with a creatinine clearance of <65 ml/min were significantly more prone to be treated with anticoagulants (17.8 vs. 14.5%, $P=0.002$) (Table 1). For all other variables we found no significant differences between groups according to creatinine clearance.

Association between creatinine clearance and number of fallers and number of falls

The multivariate analyses included predictors that have been previously shown to be associated with an increased risk of falling and that were available or variables that were significantly different between treatment groups. These variables were: age, gender, body mass index (BMI), treatment with anticoagulants and

Table 1 Comparison of the characteristics of the study participants with a creatinine clearance of <65 ml/min vs. ≥65 ml/min. **BMI* body mass index, + controlled for gender

	Categories	CrCl <65 ml/min ($n=3,238$)	CrCl ≥65 ml/min ($n=2,075$)	P-value
Gender (number)	Male/female	35.6%: 64.4%	52.7%: 47.3%	<0.0001
Age (mean ± SD)	Years	76.0 ± 6.2	70.8 ± 7.0	$<0.0001^+$
BMI* (mean ± SD)	kg/m^2	25.1 ± 3.3	27.5 ± 4.0	$<0.0001^+$
Long-term medication (in %)				
Glucocorticoid therapy		24.2%	21.9%	0.056
Anticoagulant therapy		17.8%	14.5%	0.002
Immuno-suppressive therapy		7.4%	6.8%	0.359
Vitamin D and calcium		56.7%	57.4%	0.626

glucocorticoids and total number of the daily intake of assessed medication. In this population, anti-osteoporotic treatment was not a significant predictor for falls.

The elderly men and women treated for osteoporosis with a creatinine clearance of <65 ml/min had a significantly higher risk of falls (1,775 falls in 3,238 participants vs. 773 falls in 2,075 participants; OR 1.69, 95% CI 1.50–1.91, $P<0.0001$) in multivariate controlled analyses compared to the participants with a creatinine clearance of ≥65 ml/min (Table 2). As compared to a CrCl of ≥65 ml/min a low CrCl of <65 ml/min was also associated with a significantly increased risk of being a frequent faller (% of frequent fallers according to CrCl: <65 ml/min vs. ≥65 ml/min 37.1% vs. 22.6%, OR 1.63 95% CI 1.43–1.87, $P<0.0001$) (Table 2). Other significant variables associated with the risk for falls were age ($P<0.0001$) and the number of medications ($P=0.006$). Gender or BMI were not significant predictors for falls in this study ($P=0.29$ res. $P=0.078$).

Table 2 Multivariate OR for number of falls and frequent fallers and number of fractures at different sites in elderly men and women treated for osteoporosis according to a creatinine clearance of <65 ml/min vs. a creatinine clearance of ≥65 ml/min + adjusted for age, gender, BMI, long-term treatment with anticoagulants and glucocorticoids and total number of long-term medications. $OR^{\S}$ odds ratio, CI^{II} confidence interval

Parameter	Multivariate adjusted^{+} $OR^{\S}$ (95% CI^{II})	*P*-value
Falls	1.69 (1.50–1.91)	<0.0001
Frequent fallers	1.63 (1.42–1.87)	<0.0001
Fractures		
Fracture of the femur	1.57 (1.18–2.09)	0.002
Fracture of the radius	1.79 (1.39–2.31)	<0.0001
Vertebral fractures (total)	1.31 (1.10–1.55)	0.003
Vertebral fractures (fall associated)	1.24 (1.03–1.54)	0.031

Association between creatinine clearance, number of fallers and fractures

Compared to participants with a CrCl of ≥65 ml/min, participants with a CrCl of <65 ml/min had a multivariate-adjusted significantly higher incidence of femur fractures (253/3,238 vs. 78/2,075, OR 1.57, 95%CI 1.18–2.09, $P=0.002$), a general significantly higher incidence of vertebral fractures (607/3,238 vs. 268/2,075, OR 1.31, 95%CI 1.10–1.55, $P>0.0001$), a significantly higher incidence of fall associated vertebral fractures (490/1,775 vs. 181/773, OR 1.24, 95%CI 1.03–1.54, $P=0.031$) and a significantly higher incidence of radial fractures (285/3,238 vs. 104/2,075, OR 1.79, 95%CI 1.39–2.31, $P<0.0001$) (Table 2 and Fig. 1).

Association between creatinine clearance, number of falls and long-term medication

Participants with a creatinine clearance of <65 ml/min and with no long-term medication had an increased risk for falls compared to participants with a creatinine clearance of ≥65 ml/min and no long-term medication (OR 1.78, 95% CI 1.55–2.05, $P<0.0001$).

For participants with long-term glucocorticoid treatment, a low creatinine clearance of <65 ml/min cumulatively increased the risk for falls: OR for falls in participants with a low CrCl of <65 ml/min and long-term glucorticoid treatment compared to participants with a CrCl of ≥65 ml/min and no long-term glucocorticoid treatment: OR 2.57, 95% CI 2.16–3.01/OR for falls in participants with low CrCl of <65 ml/min and long-term glucocorticoid treatment compared to participants with a CrCl of ≥65 ml/min and a long-term glucocorticoid treatment: OR 1.65, 95%CI 1.31–2.07/OR for falls in participants with a CrCl of ≥65 ml/min and a long-term glucorticoid treatment compared to participants with a CrCl of ≥65 ml/min and no long-term glucocorticoid treatment: OR 1.50, 95% CI

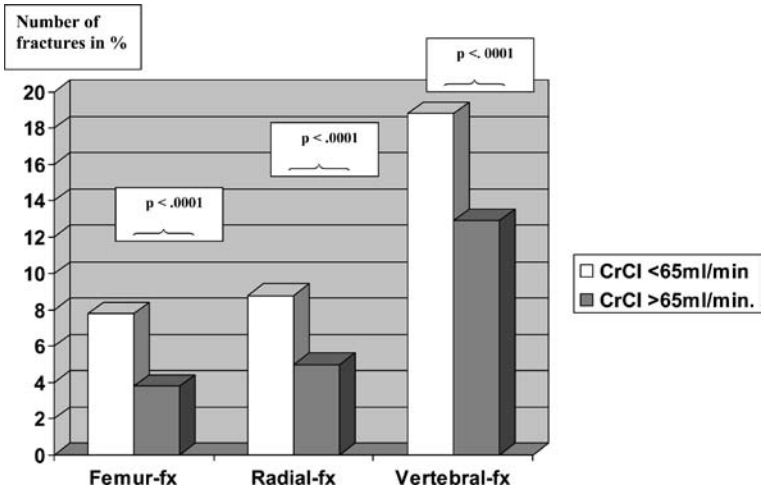

Fig. 1 Percentage of fractures (*fx*) at different sites within the last 12 months in elderly men and women treated for osteoporosis according to a creatinine clearance of <65 ml/min vs. a creatinine clearance of ≥65 ml/min

1.28–1.74, P for trend <0.001. Similar results were found for frequent fallers as well as for the other assessed long-term medications (OR for falls in participants with a CrCl of <65 ml/min and a long-term anticoagulant therapy compared to participants with a CrCl of ≥65 ml/min and a long-term anticoagulant therapy: OR 1.56, 95% CI 1.15–2.12, $P=0.005$/OR for falls in participants with a CrCl of <65 ml/min and a long-term vitamin D and calcium supplementation compared to participants with a CrCl of ≥65 ml/min and a long-term vitamin D and calcium supplementation: OR 1.91, 95% CI 1.62–2.27, $P<0.0001$/OR for falls in participants with a CrCl of <65 ml/min and a long-term immuno-suppressive therapy compared to participants with a CrCl of ≥65 ml/min and a long-term immuno-suppressive therapy: OR 2.46 95% CI 1.54–3.92, $P=0.0002$).

Association between creatinine clearance, number of fractures and long-term medication in participants experiencing falls

A history of no long-term medication in participants with a low CrCl <65 ml/min as compared to participants with a CrCl of ≥65 ml/min was associated with an increased risk for radial fractures (OR 1.37 95% CI 1.01–1.84, $P=0.040$) and no significant differences for other fracture sites. A long-term immunosuppressive therapy and a history of falls in participants with a low CrCl <65 ml/min compared to participants with a CrCl of ≥65 ml/min was associated with an increased risk for vertebral fractures (OR 3.02 95% CI 1.31–6.96, $P=0.009$) and no significant differences for other fracture sites. A long-term therapy with vitamin D and calcium and a history of falls in participants with a low CrCl <65 ml/min compared to participants with a CrCl of ≥65 ml/min was associated with an increased risk for radial fractures (OR 1.59, 95% CI 1.08–2.32, $P=0.019$) and no significant differences for other fracture sites.

In participants with a long-term anticoagulant or corticoid therapy, we found no differences in the number of fractures in participants who fell according to creatinine clearance.

Discussion

Similar to community-dwelling elderly, we found that elderly men and women treated for osteoporosis and with a low creatinine clearance of <65 ml/min have a significantly increased risk of falls and a significant increased risk of frequent falls compared to elderly men and women treated for osteoporosis and with a creatinine clearance of ≥65 ml/min. Furthermore, a creatinine clearance of <65 ml/min was compared to CrCl of ≥65 ml/min in these elderly men and women treated for osteoporosis associated with a significant increased risk of total vertebral fractures, with a significant increased risk of fall-associated vertebral fractures and with a significant increased risk of hip and radial fractures. The fact that hip and radius fractures are mainly fall-induced is accepted world-wide [18] and has been confirmed, but our result that vertebral fractures are also partly induced by falls is new and to our knowledge has never been described in the literature. A low creatinine clearance of <65 ml/min together with long-term therapies such as glucocorticoid, immunosuppressive and anticoagulant treatments, which have been previously described as increasing the risk of osteoporosis [23, 24, 25, 26], increases the risk for falls and fractures cumulatively in these elderly men and women treated for osteoporosis. The incidence of falls and fractures increases rapidly after the first 3 months and reverts sharply towards baseline after discontinuation of oral glucocorticoid treatment [23]. Immunosuppressive drugs are given to patients with chronic inflammatory diseases. In these diseases circulating cytokines interfere with bone and muscle metabolism and induce a significant risk for secondary osteoporosis, muscle atrophy and fractures [27, 28, 29]. Interestingly, in this study group a long-term therapy with vitamin D and calcium was not associated with a decreased risk for falls in participants with a low creatinine clearance of <65 ml/min, but was contrarily associated with an increased risk for falls and an increased risk for radial fractures. However, this result should be interpreted with caution since we don't have any data on the amount and the duration of the supplementation of calcium and vitamin D and no information on compliance, i.e., measured as calcidiol serum levels. In a recently published, randomized, double-blind placebo-controlled study in the elderly aged over 80 years it has been shown that a single oral dose of 300,000 IU plain vitamin D over 6 months failed to reduce the fall rate, even in those who were vitamin D deficient (<12 ng/ml) at baseline and after normalization of the 25(OH)D levels [30]. A confirmative, placebo-controlled clinical study including 10,000 community-dwelling elderly women and men has recently proven that an annual intramuscular application of 300,000 IU plain vitamin D is not able to reduce the risk of falls and hip or other non-vertebral fractures [31]. However, in another study the supplementation of vitamin D and calcium was found to significantly reduce the number of falls in institutionalized elderly women with vitamin D deficiency [50]. All these findings support our theory that below a creatinine clearance of <65 ml/min, calcidiol is not metabolized to calcitriol, the most active form of vitamin D. In a significant number of osteoporotic people, even with normal vitamin D serum levels (>12 ng/ml), a deterioration of renal function, easily measurable as deterioration of the creatinine clearance, leads to decreased activity of the renal 1α-hydroxylase [10, 32] and consecutively to low D-hormone serum levels [33, 34, 35], as observed in age-related impaired renal function [20], with drug interaction (i.e., glucocorticoid and immunosuppressive treatment) or in chronic inflammatory diseases. Nuclear factor κB (NFκB) and tumor necrosis factor (TNF)-α inhibit the renal

1α-hydroxylation of 25(OH)D [36], which explains the decreased serum concentration of D-hormone in chronic inflammatory diseases depending on disease activity [37]. D-hormone has a scientifically established effect on muscle strength, balance and functional mobility [3, 4, 5, 6, 7, 8, 9]. In several studies [38, 39] the effect of D-hormone treatment (alfacalcidol res. calcitriol) on the risk of falls has been proven. Furthermore, it has been shown that treatment with alfacalcidol in community-dwelling elderly men and women with a low CrCl of < 65 ml/min significantly decreases the low CrCl-associated high risk for falls [2]. The increased osteopenia and osteoporosis observed with low creatinine clearance by other authors [19, 20] may also be due to the low D-hormone serum levels observed with a creatinine clearance of < 65 ml/min. Our result enhances the theory suggested by other studies [4, 5, 6, 7, 32, 34, 35, 40, 41, 42] that low D-hormone is an independent risk factor for falls [5, 38, 39, 42] and that D-hormone is directly involved in the causal pathogenic pathway of decreased muscle strength related falls [9, 43, 44, 45].

Histochemical classification of the muscle fiber composition based on muscle biopsies revealed that a treatment of osteoporotic patients with alfacalcidol (1 μg daily) for 3 to 6 months induced a significant increase in the relative number of fast-twitch type II fibers [9]. In addition there was an increase in the cross-sectional area of this muscle fiber type that is responsible for fast reaction and which is decreased in older age [9].

D-hormone receptors (VDRs) have been found in skeletal muscles and nerves [46] through which muscle contraction and relaxation are controlled by the influx and efflux of calcium and in addition the muscle protein synthesis [43]. It has been recently confirmed in VDR gene-deleted mice that the absence of VDRs causes a reduction of skeletal muscle fiber size based on an increased expression of myogenic regulation factors (Myf5, myogenin, E2A) through which the strictly regulated differentiation and maturation of muscle cells are disturbed [45]. The muscular abnormalities are independent from secondary, metabolic changes, e.g., hypocalcemia or hyperparathyroidism. This confirms the direct efficacy of VDRs. The fact that a treatment with D-hormone of VDR-positive myoblasts in vitro down-regulates the mentioned myoregulating transcription factors points out in addition the important role of D-hormone and VDRs in muscle development [45]. Older age is significantly associated with decreased VDR expression in human skeletal muscle tissue [47], and a positive correlation was found between femoral muscle strength and function and D-hormone serum levels in the elderly [4, 8]. These results suggest that the age-related decline in muscle strength and function and the increase of falls could be explained in part by a decrease of VDRs and a decrease of D-hormone in serum and/or at the receptor level.

We therefore conclude that our observed increased risk of falls in elderly men and women treated for osteoporosis with a low creatinine clearance of < 65 ml/min is due to a creatinine clearance-dependent decrease in D-hormone serum levels. Our finding that a long-term treatment with vitamin D and calcium in osteoporotic men and women with a CrCl of < 65 ml/min is associated with an increased risk for falls suggests that the only treatment option for osteoporotic men and women with a low CrCl of < 65 ml/min, in order to prevent falls and fall-associated fractures and in order to treat the metabolic low D-hormone syndrome, are D-hormone analogs such as calcitriol or alfacalcidol. The rationale for this conclusion is the accepted scientific knowledge that D-hormone analogs can act without metabolic activation in the kidney, which results in higher concentrations of D-hormone at the receptors of the target organs [48]. The difference between plain vitamin D and D-hormone analogs on low creatinine clearance-related falls can be explained by the known fact that the expression of D-hormone receptor occurs only in the presence of D-hormone, not in the presence of plain vitamin D. It can be hypothesized that an increased expression of the D-hormone receptors in the muscle, in neurons and in the brain leads to an improvement of muscle power and an improvement of fall-related neuronal functions, e.g., increased balance performance, increased muscle coordination and increased cognitive capabilities, which all would result in a reduction of falls. Serum levels of calcitriol, but not of calcidiol, have been found to be significantly correlated with cognitive function in elderly women [49].

We furthermore found that elderly men and women treated for osteoporosis with long-term treatments known to increase the risk of osteoporotic fractures, such as long-term treatment with immuno-suppressive therapy, long-term corticosteroid treatment and long-term anticoagulant treatment, are at greater risk for falls and fractures when these long-term treatments are combined with a low CrCl of < 65 ml/min. Physicians should therefore pay special attention to patients with such long-term treatment and assess the creatinine clearance in order to diagnose high risk patients for falls and fractures and treat them accordingly.

Our study has several limitations. The results are from a cross-sectional study with its well-known limitations of interpretation. The primary outcome variable "falls" was assessed by recall with the inherent recall bias. Another limitation is that falls were not defined, and physicians were not instructed in the assessment of falls. Therefore, we cannot rule out some miss-classification in the outcome variable falls, in the sense that some non-locomotoric extrinsic falls [i.e., due to some specific physical activities (skiing, cycling) or accidents (being run over by a dog or child)] or due to syncopal falls were assessed as locomotoric intrinsic falls. However, we assume that the incidence of extrinsic or syncopal falls is independent from creatinine clearance and does not influence the validity of our result. Concerning the fall-associated fractures, we also did not assess the history of fractures, which would have been an important control variable for this outcome variable. We could also not control for

other important covariates such as comorbid conditions, number of medications, physical activity and other not-assessed control variables. Therefore, we cannot rule out uncontrolled confounding. Furthermore, the diagnosis of osteoporosis was solely based on the physician's report. We can therefore not rule out a misclassification concerning the diagnosis of osteoporosis. We can assume that this possible misclassification concerns the whole study group and does not influence our result on the influence of a low creatinine clearance on the frequency of falls and fractures in this population. The participants were Caucasian elderly men and women over the age of 65 treated for osteoporosis. The diagnosis of osteoporosis was not based on BMD for all participants. Therefore, our findings cannot be generalized to a general osteoporotic population, to a younger population or to osteoporotic men and women of other races.

In conclusion, in this observational study a low creatinine clearance of <65 ml/min in elderly men and women treated for osteoporosis was associated with an increased risk of falls, an increased risk of frequent falls and an increased risk of total vertebral fractures, fall-associated vertebral fractures, hip and radial fractures. Randomized controlled studies are needed to confirm our findings.

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