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Full Length Article

Thoracic vertebral fractures and hyperkyphosis in elderly patients with end-stage kidney disease; do these patients have different clinical outcomes?

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ABSTRACT

Background and objectives: Elderly patients with end-stage kidney disease (ESKD) are at high risk for fractures. However, the prevalence of vertebral fractures and hyperkyphosis is not studied well. This is relevant, because in the general population, both vertebral fractures and hyperkyphosis are associated with poor outcome. Therefore, the primary aim of our study was to assess the prevalence of vertebral fractures and hyperkyphosis in the ESKD population. The secondary aim was to assess if patients with vertebral fractures and/or hyperkyphosis more often have poor outcome after starting dialysis, such as accidental falling, functional decline and mortality compared to the patients without vertebral fractures and/or hyperkyphosis.

Design, setting, participants & measurements: This study included patients ≥65 years with ESKD who were enrolled in the Geriatric assessment in Older patients starting Dialysis (GOLD) study of whom a lateral chest radiograph was available. Chest radiographs were scored independently by two observers for vertebral fractures (Genant ≥1) and hyperkyphosis (≥50 degrees). The relation between vertebral fractures and hyperkyphosis with clinical outcomes (falls, decline in ADL and IADL, mortality) was studied using the Chi-square test.

Results: Of the 196 enrolled patients, chest radiographs were available for 160 patients. Mean age was 75.3 (SD ± 6.9), and 35% were female. The prevalence of vertebral fractures was 43% and of hyperkyphosis 22%. Patients with hyperkyphosis had a higher one-year mortality compared to patients without hyperkyphosis (20% vs. 8%, p = 0.04). No differences were observed between patients with and without hyperkyphosis, vertebral fractures and the remaining outcomes after six months of follow-up.

Conclusions: In patients ≥65 years old with ESKD starting dialysis, vertebral fractures are highly prevalent. In contrast to the general population, patients with vertebral fractures did experience poor outcome as often as patients without vertebral fractures. Remarkably, patients with hyperkyphosis did have a higher one-year mortality. However, these patients did not experience more functional decline or accidental falls.

1. Introduction

In the Western world, approximately 40% of the population with end-stage kidney disease (ESKD) is older than 65 years [1,2]. Both age and ESKD are associated with an increased risk of fractures [3]. Elderly ESKD patients are more prone to falls, due to decreased postural reflexes [4], neurological and cardiovascular comorbidity and neurosensory impairment [5]. Besides a higher risk of falls, osteodystrophy and osteoporosis increase the risk of fracture even further. For example, previous research showed a four times higher risk of hip fractures when patients were treated with dialysis compared to patients of the same age without ESKD [6–8]. However, the prevalence of vertebral fractures in patients with ESKD has a broad range with prevalence ranging from 10 to 55% [9–15].

Abbreviations: ESKD, end-stage kidney disease

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In regular care of patients with ESKD, a chest radiograph is commonly performed. Besides amount of fluid retention and infection, these radiographs can also provide information about the condition of a large proportion of the vertebrae. Furthermore, these radiographs can be used to measure the kyphosis angle of the thoracic spine. Previous research in the non-ESKD population showed that vertebral fractures could lead to back pain [16], future fractures [17], reduced physical performance [18] and an increased curvature of the thoracic spine in the sagittal plane (thoracic hyperkyphosis) [19]. Furthermore, both vertebral fractures and hyperkyphosis are associated with an increased mortality [16,20]. Based on this information, it is possible that vertebral fractures and hyperkyphosis in elderly patients with ESKD who are initiating dialysis are also associated with poor outcome. If vertebral fractures and/or hyperkyphosis are associated with poor outcome, these could provide an opportunity to improve decision-making considering dialysis in the elderly patient with ESKD.

Therefore, the primary aim of the current study was to evaluate the prevalence of vertebral fractures and hyperkyphosis on lateral chest radiographs in a population with end-stage kidney disease initiating dialysis; the secondary aim was to assess if patients with vertebral fractures or hyperkyphosis more often experience poor outcome such as accidental falling, functional decline and mortality.

2. Materials and methods

2.1. Study participants

Data were used from the Geriatric assessment in Older patients starting dialysis (GOLD) study. This is a multicenter, prospective cohort study assessing the relation between a geriatric assessment and outcome in patients with end-stage kidney disease (ESKD). The study was also designed to assess the prevalence of vertebral fractures, accidental falls and functional change in elderly patients initiating dialysis. Participants were enrolled from 17 centers across the Netherlands in the period from August 2014 to September 2017. Patients initiating dialysis (peritoneal dialysis (PD) and hemodialysis (HD)) who were ≥ 65 years were included. Patients were recruited from the pre-dialysis outpatients clinics by their treating nephrologists. The aim was to include patients eligible for dialysis between 3 weeks before and 2 weeks after dialysis initiation. Patients were excluded if informed consent was not provided, if they had insufficient understanding of the Dutch language, or if they suffered from a terminal nonrenal-related condition. If inclusion criteria were met, patients were contacted by one of the researchers or research nurses to make an appointment for inclusion. After six months patients were contacted by telephone for follow up. Furthermore, data on six-month mortality was collected from each center. Because six-month mortality was lower than expected, we decided to extend the follow-up of mortality to one year.

The study was conducted in accordance with the declaration of Helsinki and approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients before enrollment.

2.2. Data collection

2.2.1. Baseline

For the geriatric assessment, participants were either visited at home (on a nondialysis day for patients on hemodialysis) or in the dialysis center before starting the dialysis session. The assessments were performed by one of the investigators (N.G., I.v.L) or one of the trained research nurses. Baseline demographic data collected from the medical charts and during the geriatric assessment included age, sex, living situation and number of medications. Other clinical characteristics included cause of kidney failure, dialysis modality, body mass index (BMI), intoxications (alcohol use, smoking habit) and laboratory results (albumin, phosphate, PTH and calcium). Functional performance was assessed using the Katz-6 scale for basic activities of daily living (ADL) [21] and the Lawton & Brody scale for instrumental activities of daily living (IADL) [22]. An impaired (I)ADL was defined as one or more impaired items. The cumulative incidence rating scale for geriatrics (CIRS-G) was assessed as a measure for co-morbidity burden based on the patients' medical charts [23]. Severe comorbidity burden was defined as ≥2× score 3 or ≥1× score 4. Mobility was measured by the Timed Up and Go test (TUG). If the TUG was completed in < 10 s, mobility was considered normal, 10 to 20 s was defined as mildly impaired and > 20 s as severely impaired [24]. The cognitive function of the participants was assessed through the Mini Mental State Examination (MMSE) [25]. Cognitive impairment was defined as an MMSE score lower than 25. For depression the Geriatric depression scale 15 'GDS-15' was used. Depression was defined as a score above 5 [26].

To assess frailty the Fried Frailty Index was used [27]. This is a 5-item questionnaire that assesses malnutrition (unintentional weight loss ≥4.5 kg or ≥5% body mass in the last year), exhaustion (self-report), weakness (reduced handgrip strength [28]), slow gait (≥6 s for 4 m) and low physical activity (men < 393 kcal/week; women < 280 kcal/week). A score of 3 or more was considered as frail [27].

2.2.2. Follow-up

All patients alive six months after inclusion were interviewed by phone by a research nurse or investigator. During this interview, questionnaires about functional status (ADL, IADL) were completed. For baseline and follow-up, the number of functional dependencies in ADL and IADL were counted. If there were more dependencies (≥1) at follow-up in ADL or IADL, this was defined as functional decline.

Furthermore, patients were interviewed about accidental falls. Falls were defined according to the World Health Organization as 'an event which results in a person coming to rest inadvertently on the ground or floor or other lower level' [29]. Frequent falls were defined as two or more accidental falls. When patients had fallen, but no number of falls was available, this was scored as less than two falls.

2.3. Diagnosis of vertebral fractures

A lateral chest radiograph was taken in the period of six months before or six months after initiation of dialysis of each dialysis patient. Although this was part of the study design, most radiographs were already performed in regular care. In two centers (29 participants) there was no financial agreement on the costs of performing a chest radiograph. Therefore, in these centers, only chest radiographs that were performed in regular care were used for assessment. Every lateral chest radiograph was scored independently by two observers (NG, MK) for vertebral fractures. Chest radiographs were analyzed by using the semi-quantitative method of Genant [30]. All radiographs were re-read in consensus readings and verified by an expert geriatrician (HW). If case findings were different, defined as a different Genant score or a difference between the presence of vertebral fractures, the diagnosis of the expert (HW) was considered as gold standard. In 42 out of 1775 assessable vertebrae (2%) the diagnosis of the third observer led to a different score. Fractures were categorized by severity: grade 1 (20–25% loss of height), grade 2 (25–40% loss of height) and grade 3 (> 40% loss of height).

Based on Genant scores a summary number for the severity and the number of the vertebral fractures was calculated by dividing the sum of the abnormal grades by the number of vertebrae that could be assessed per patient. For example, a patient with a grade 2 and a grade 3, with 11 assessable vertebrae, gives a score of ((2 + 3) / 11 = 0.45).

2.4. Kyphosis measurement

To quantify the thoracic kyphosis, the modified Cobb angle was used [31]. This is the angle measured between the superior endplate of the 4th and the inferior endplate of the 12th thoracic vertebrae.

Hyperkyphosis was defined as an angle of 50 degrees or higher. This is one of the most commonly used cut-off values in elderly patients [32,33].

2.5. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (version 25.0 for Windows, SPSS, Inc., Chicago IL.). Included patients were compared with excluded patients (patients in whom no chest radiograph was available) for baseline characteristics. Furthermore, we compared patients with vertebral fractures (grade ≥1) on the chest radiograph with patients with no vertebral fractures and patient with hyperkyphosis with patients with normal kyphosis angle for baseline characteristics and outcome (accidental falling, functional decline, mortality). Differences between groups were evaluated using the Chi-square test for categorical variables or the Fisher exact test in case of low number of events (n ≤ 5), independent *t*-tests for continuous variables that were normally distributed and Wilcoxon rank sum test for non-parametric continuous data. The association between severity of vertebral fractures (summary score) and grade of kyphosis angle was assessed by using univariate linear regression. Categorical data were reported as proportions, continuous variables were reported as mean with standard deviation (SD) or median with interquartile range (IQR). A two-sided probability of $p < 0.05$ was considered statistically significant. Outcomes were calculated with a 95% confidence interval (95% CI).

3. Results

3.1. Baseline characteristics

This analysis includes all incident dialysis patients included in the GOLD-study (n = 196) of whom a lateral chest radiograph was available (n = 160). Baseline data of excluded incident dialysis patients (n = 36) is shown in Appendix 1. No differences were found in baseline data between included and excluded patients. The mean age of the included patients was 75.3 (SD ± 6.9), and 35% were female. The majority of the patients was living at home (94%). The main cause of end-stage kidney disease was vascular disease (53%), followed by diabetes (14%). At baseline, 29% of the patients was dependent in ADL and 80% was dependent in IADL. Most frequently impaired domains in ADL were bathing (18%), incontinence (18%) and dressing (14%). Most frequently impaired domains in IADL were doing laundry (53%), medication use (46%) and housekeeping (44%). Regarding mobility, 63% was not able to perform the Timed up and Go test within 10 s (of whom 8 patients (5%) were immobile). Sixty-six percent of the patients was considered frail according to the Fried Frailty Index.

3.2. Prevalence of vertebral fractures

A mean of 11 (SD ± 1.4) vertebrae could be analyzed per patient. Of all patients, 68 (43%) had one or more vertebral fractures (median 1.0, IQR 1.0). Highest grade of fracture per patient were Genant 1 in 36 patients (23%), Genant 2 in 25 patients (16%) and Genant 3 in 7 patients (4%). Of all fractures, most frequently fractured vertebrae were the 7th thoracic vertebra (16%), the 12th (9%) and the 8th thoracic vertebra (6%). Baseline data for the included patients are shown in Table 1. Patients with vertebral fractures were more impaired in ADL (40% vs. 21% in patients without vertebral fractures, p = 0.01). No differences were seen in demographics, medical history, additional measurements (BMI, TUG, symptoms of depression, impaired cognition, impaired (I)ADL), laboratory results and frailty measurement. Baseline data for more severe fractures (Genant ≥2) are shown in Appendix 3.

3.3. Prevalence of hyperkyphosis

Baseline characteristics of participants with and without hyperkyphosis are shown in Table 1. Of all patients, 35 (22%) had hyperkyphosis (defined as a Cobbs angle of ≥50 degrees). Compared to the patients without hyperkyphosis, patients with hyperkyphosis were more frequently female (50% vs. 30%, p = 0.02), had a lower BMI (median 24.1 (IQR 5.8) vs. median 26.3 (IQR 6.8), p = 0.04) and more patients experienced accidental falls in the six months before inclusion (45% vs. 25%, p = 0.03). Furthermore, patients were more impaired in ADL at baseline (46% vs. 24%, p = 0.01) and were more frequently living in a nursing home (14% vs. 3%, p = 0.01).

3.4. Relation between severity of vertebral fractures and kyphosis

The mean severity score of vertebral fractures was 0.09 (SD 0.17) and the mean kyphosis angle 41.00 (SD 10.84). A higher vertebral severity score was associated with a larger kyphosis angle (B 21.35, 95% CI 12.1–30.6, p ≤ 0.001). This explained 11.6% of the variance of the degree of kyphosis.

3.5. Outcome after six months and one year

Outcome data on mortality were available for all patients (n = 160) and data on functional decline and accidental falling for 144 patients (Table 2). Six patients were lost to follow-up. After six months of follow-up, 10 of the included patients died and 3 patients received a kidney transplant. Of the patients still alive after six months, 27 (18%) declined in ADL and 65 (42%) patients declined in IADL. Domains that declined most were doing laundry (60% vs. 53% at baseline, p = 0.05) and self-administering medications independently (57% vs. 46%, p = 0.02) (Appendix 2). Forty-one patients (26%) experienced a fall in the six months after initiation of dialysis. Of these patients, 13 patients experienced ≥2 falls. After one year of follow-up another 7 patients had died (total of 17 patients).

Patients with hyperkyphosis had a higher one year mortality compared to patients without hyperkyphosis (20% vs. 8%, p = 0.04). No differences were seen in outcome when comparing patients with vertebral fractures to patients without vertebral fractures.

3.6. Relation between vertebral fractures, hyperkyphosis and outcome variables (accidental falls, functional outcome and mortality)

Fig. 1 shows the distribution of patients per outcome (accidental falling, functional decline, six-month and one-year mortality) the proportion of patients with hyperkyphosis, vertebral fractures or both. For patients that died within six months, no follow-up data was available on accidental falling and decline in ADL and IADL. Of the included patients, 24 (16%) patients had both hyperkyphosis and vertebral fractures and 81 patients (51%) had no vertebral fractures and no hyperkyphosis. Of the 24 patients with both hyperkyphosis and vertebral fractures 29% died within one year (compared to 0% for patients with only hyperkyphosis, 5% for patients with only vertebral fractures and 10% with no vertebral fractures and no hyperkyphosis, p = 0.02). Data on one-year mortality, hyperkyphosis and vertebral fractures is shown in Table 3. Accidental falling and functional decline were not associated with the presence of hyperkyphosis or vertebral fractures.

4. Discussion

In this prospective multicenter cohort study of 160 elderly incident dialysis patients, 43% of the patients had vertebral fractures, 22% had hyperkyphosis, and 16% had both vertebral fractures and hyperkyphosis. After six months of follow-up, patients with vertebral fractures and/or hyperkyphosis experienced functional decline, accidental falling and mortality as often as patients without vertebral fractures or

Table 1
Baseline characteristics vertebral fractures (Genant ≥1) vs. no fractures and hyperkyphosis vs. normal angle.

	Vertebral fracture (n = 68)	No/mild fractures (n = 92)	p value	Hyperkyphosis (n = 35)	Normal kyphosis (n = 125)	p value
Demographics						
Age, (mean, SD)	75.2 (6.9)	75.4 (6.9)	0.82	76.9 (7.3)	74.9 (6.7)	0.14
Female, n (%)	21 (31%)	35 (38%)	0.35	18 (50%)	38 (30%)	**0.02**
Single/widow	40 (59%)	50 (54%)	0.57	18 (51%)	72 (57%)	0.52
Living at nursing home	5 (7%)	4 (4%)	0.42	5 (14%)	4 (3%)	**0.01**
Intoxications						
Smoker[a]	48 (75%)	66 (75%)	1.00	22 (67%)	92 (77%)	0.21
Alcohol use	27 (43%)	34 (39%)	0.60	15 (46%)	46 (39%)	0.50
Medical history						
Severe comorbidity burden[b]	29 (43%)	41 (45%)	0.81	14 (40%)	56 (45%)	0.61
Number of medications (median, IQR)	11.5 (6.8)	11.5 (5.0)	0.24	11.0 (7.0)	12.0 (6.0)	0.49
Underlying kidney disease						
Diabetes	8 (12%)	14 (15%)	0.42	2 (6%)	20 (16%)	0.22
Vascular	35 (41%)	50 (54%)		21 (60%)	64 (51%)	
Glomerulonephritis	6 (9%)	1 (1%)		0 (0%)	7 (6%)	
Interstitial nephropathy	1 (2%)	2 (2%)		2 (6%)	1 (1%)	
Polycystic kidney disease	3 (4%)	4 (4%)		2 (6%)	5 (4%)	
Other/unknown	15 (22%)	21 (23%)		8 (22%)	28 (22%)	
Hemodialysis[c]	51 (75%)	69 (75%)	1.00	27 (77%)	93 (74%)	0.74
Additional measurements/tests/questionnaires						
BMI (median, IQR)	25.9 (6.0)	26.7 (7.5)	0.61	24.1 (5.8)	26.3 (6.8)	**0.04**
Timed-up-and-go-test (in seconds)						
< 10 (normal mobility)	21 (33%)	31 (35%)	0.37	12 (36%)	40 (34%)	0.14
10–20 (mildly impaired mobility)	27 (42%)	43 (49%)		11 (33%)	59 (50%)	
> 20 (severely impaired mobility/ immobile)	16 (25%)	14 (16%)		10 (30%)	20 (17%)	
≥1 accidental falls (previous 6 months)	22 (37%)	20 (24%)	0.09	14 (45%)	28 (25%)	**0.03**
Symptoms of depression (GDS ≥ 5)	22 (32%)	25 (27%)	0.48	9 (26%)	38 (30%)	0.59
Impaired cognition (MMSE < 25)	9 (13%)	13 (15%)	0.81	7 (20%)	15 (13%)	0.26
Impaired ADL at baseline (≥1)	27 (40%)	19 (21%)	**0.01**	16 (46%)	30 (24%)	**0.01**
Impaired IADL at baseline (≥1)	53 (78%)	75 (82%)	0.58	28 (80%)	100 (80%)	1.00
Laboratorium						
Hemoglobin (mean, SD)	6.6 (0.9)	6.4 (1.0)	0.20	6.5 (0.7)	6.5 (1.0)	0.71
Albumin (median, IQR)	34.3 (9.6)	34.0 (7.0)	0.33	34.0 (5.2)	34.4 (9.0)	0.60
Bicarbonate (mean, SD)	20.3 (4.3)	20.7 (5.0)	0.69	19.9 (5.3)	20.7 (4.5)	0.40
PTH (median, IQR)	25.6 (32.9)	27.4 (29.9)	0.74	26.1 (31.9)	27.7 (31.3)	0.89
Calcium (mean, SD)	2.2 (0.2)	2.2 (0.2)	0.22	2.3 (0.2)	2.2 (0.2)	**0.04**
Phosphate (mean, SD)	1.7 (0.6)	1.7 (0.6)	0.45	1.6 (0.4)	1.8 (0.6)	0.07
Frailty measurements						
Impaired Fried frailty Index	26 (41%)	40 (46%)	0.61	19 (58%)	47 (40%)	0.07

ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, mini mental state examination; GDS, geriatric depression scale.
Bold values statistically significant at $p < 0.05$.
[a] Smoker.
[b] Cumulative illness rating scale for geriatrics (CIRS-G) of ≥2× score 3 or ≥1× score 4.
[c] The other patients started peritoneal dialysis.

hyperkyphosis. Remarkably, after one year of follow-up, 20% of the patients with hyperkyphosis had died compared to 8% of the patients without hyperkyphosis. This mainly concerns the 24 patients with both hyperkyphosis and vertebral fractures of whom 29% died within one year.

The prevalence of vertebral fractures in our study was in the upper range compared to previous studies in the elderly dialysis population (mean age ranging from 64 to 72 years) that have found a prevalence ranging from 10 to 55% [9–12,14,34]. However, study results are difficult to compare because of the use of different methods to assess vertebral fractures, different cut-off values to define fractures (> 20% vs. > 25%), and the amount of vertebrae assessed. Interestingly, a Dutch population based cohort study with a comparable age (mean 75.8 years) has found a prevalence of vertebral fractures of 47% [35]. This is strikingly similar to the prevalence in our dialysis population (43%), particularly considering that only 1% of this population based

Table 2
Outcomes for vertebral fractures (Genant ≥1) vs. no fractures and hyperkyphosis vs. normal angle.

	Vertebral fracture (n = 62)	No vertebral fracture (n = 83)	p value	Hyperkyphosis (n = 35)	Normal kyphosis (n = 124)	p value
Accidental falling	20 (32%)	21 (26%)	0.44	11 (34%)	30 (27%)	0.40
Decline in ADL	10 (16%)	52 (44%)	0.51	5 (16%)	22 (19%)	0.69
Decline in IADL	29 (47%)	36 (43%)	0.68	17 (55%)	48 (42%)	0.21
Mortality 6 months	5 (7%)	5 (5%)	0.62	4 (11%)	6 (5%)	0.15
Mortality 12 months	9 (13%)	8 (9%)	0.36	7 (20%)	10 (8%)	**0.04**

ADL, activities of daily living; IADL, instrumental activities of daily living. p value reflects the result of a Chi-Square test.
Bold value statistically significant at $p < 0.05$.

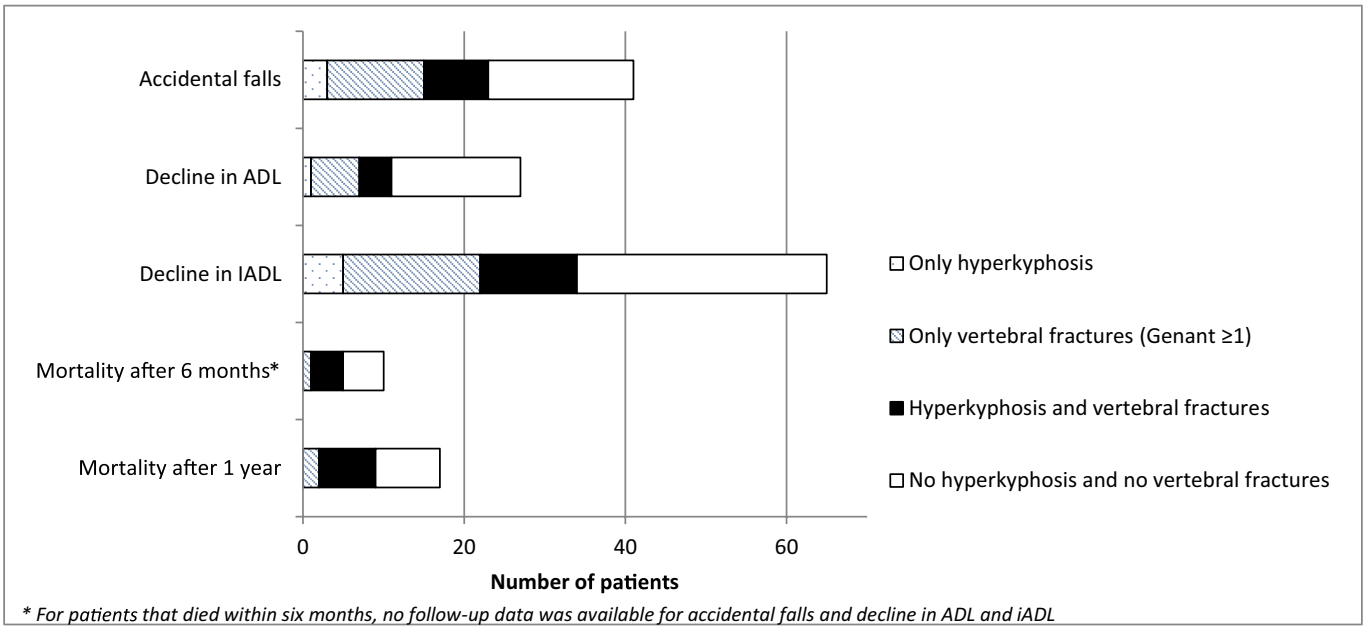

Fig. 1. Distribution of patients according to vertebral fractures (Genant ≥1), hyperkyphosis, functional decline, accidental falls and mortality.

cohort had stage 5 kidney disease [35] and 30% of had an eGFR < 60 ml/min [35]. As bone abnormalities worsen when eGFR decreases [36], we expected a higher vertebral fracture prevalence in patients with ESKD initiating dialysis than in the general population. Our lower prevalence is probably caused by the use of only thoracic chest radiographs for assessing vertebral fractures whereas the population based study used both thoracic and lumbar radiographs. Therefore, our study may have underestimated the number of lumbar vertebral fractures. On the other hand, bone abnormalities of chronic kidney disease may be more severe in cortical bone [37]. As a large part of the vertebrae consist of trabecular bone, this may account for the similar prevalence of vertebral fractures at the initiation of dialysis.

Compared to the general elderly population, the prevalence of hyperkyphosis that we have found was also lower than expected. Prior research estimated the prevalence of hyperkyphosis in the elderly population between 20 and 55% [33,38–40], of which only the study of van der Jagt et al. used a similar method to diagnose hyperkyphosis [33] No literature could be found on the prevalence of hyperkyphosis in patients with kidney disease. As severe hyperkyphosis can already be seen without additional imaging, it is possible that patients with severe hyperkyphosis are more frequently labeled as frail, and therefore less likely to initiate dialysis. Furthermore, as patients who have worse health may have been less likely to participate in this study, this could have led to a relatively healthy ESKD population. Both could have led to a relatively low prevalence of hyperkyphosis.

To our best knowledge, no previous research assessed the association between vertebral fractures, falls and functional decline in the ESKD population. However, there were two studies that assessed the relation between vertebral fractures and mortality in patients treated by hemodialysis [10,34]. One study found an association between vertebral fractures and a higher two-year mortality in women treated by hemodialysis [34] and the other study showed this for both women and men, but by only assessing lumbar vertebral fractures [10]. In contrast to these studies and studies in the general population [18], we did not found an association between vertebral fractures and poor outcome. A possible explanation may be that the initiation of dialysis had such a big impact, that other risk factors (such as vertebral fractures) were less important for prognosis in the first year after start of dialysis. Furthermore, no follow-up data on accidental falls and functional decline was available for patients that died within six months. As elderly patients frequently deteriorate in physical function before death [41], it is well possible that these patients experienced a fall or showed functional decline before death. This could have led to an underestimation of falls and functional decline which could have obscured a potential association between vertebral fractures and poor outcome could have been missed.

Interestingly, despite the low event rate of death, we did find a higher one-year mortality after start of dialysis in patients with hyperkyphosis. Considering every patient that died with hyperkyphosis had also vertebral fractures, and only 12% of the variance of the degree of kyphosis was explained by severity of vertebral fractures, the combination of both vertebral fractures and hyperkyphosis seems to be important for predicting mortality. Unfortunately, because of no mortality events in the only hyperkyphosis group, no additional analysis could be performed to assess a possible interaction between hyperkyphosis and vertebral fractures. Our study findings are in agreement with a previous study in the general population that showed that in older women with vertebral fractures, hyperkyphosis was a risk factor for death [20]. A possible reason for this association could be that hyperkyphosis (possibly in combination with vertebral fractures) could be an indicator of physical dysfunction [42], such as a decrease in muscle mass and muscle strength, what could lead to frailty and subsequently poor outcome [43]. This was also observed in our study population as patients with hyperkyphosis tended to be more frail according to the Fried Frailty Index. Furthermore, they were more dependent on care and were more likely to experience accidental falls compared to patients without hyperkyphosis. These are all known risk factors for poor outcome in the ESKD-population [5]. Therefore, it could be beneficial to perform additional frailty screening and optimization of physical performance in the patients with both hyperkyphosis and vertebral fractures.

The major strength of this study is a large multicenter cohort study where vertebral fractures were diagnosed by the use of radiographs, instead of using ICD-codes or medical history. Limitations are that we used a radiograph of the chest to diagnose vertebral fractures. Because this type of imaging only provides information on the first few lumbar vertebrae, this could have led to an underestimation of vertebral fractures. Second, due to low rate of events, and therefore lack of power in

Table 3
Relation between vertebral fractures, hyperkyphosis and one-year mortality.

	Vertebral fracture and hyperkyphosis (n = 24)	Only hyperkyphosis (n = 11)	Only vertebral fractures (n = 44)	No vertebral fractures and no hyperkyphosis (n = 81)	p value
Alive after one year (n, %)	17 (71%)	11 (100%)	42 (96%)	73 (90%)	0.02
Death within one year (n, %)	7 (29%)	0 (0%)	2 (5%)	8 (10%)	

p value reflects the result of the Fisher's Exact Test.

the study, it is possible that we have missed a potential association between vertebral fractures, hyperkyphosis and poor outcome. Furthermore, we could not perform regression analysis to adjust for potential confounders. Third, as patients with worse health were less likely to participate, the results that we have shown for the prevalence of vertebral fractures and hyperkyphosis are possibly not fully generalizable to all elderly initiating dialysis.

In conclusion, in patients ≥65 years with ESKD that are initiating dialysis, vertebral fractures are highly prevalent. In contrast to the general population, patients with vertebral fractures did not experience more often poor outcome. Remarkably, patients with hyperkyphosis did experience a higher one-year mortality. Considering these patients were also more frequently frail and dependent of care, especially in these patients additional frailty screening and optimization strategies of physical performance before initiation of dialysis could be beneficial. More research in larger cohorts is needed to better quantify the risk of poor outcome in ESKD patients with vertebral fractures and hyperkyphosis.

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CRediT authorship contribution statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.06.007.

References

[1] United States Renal Data System, 2017 USRDS annual data report: epidemiology of kidney disease in the United States. [internet]. Vol. 1. Bethesda, Available from: https://www.usrds.org/2017/download/2017_Volume_1_CKD_in_the_US.pdf.

[2] T. Hoekstra, F.J. Van Ittersum, M.H. Hemmelder, RENINE annual report 2017, Available from: https://www.nefrovisie.nl/wp-content/uploads/2018/12/RENINE-year-report2017-web.pdf.

[3] F. Pouresmaeili, B. Kamali Dehghan, M. Kamarehei, G. Yong Meng, A comprehensive overview on osteoporosis and its risk factors, Ther. Clin. Risk Manag. Volume 14 (2018) 2029–2049.

[4] J. Magnard, J. Lardy, A. Testa, D. Hristea, T. Deschamps, The effect of hemodialysis session on postural strategies in older end-stage renal disease patients, Hemodial. Int. 19 (4) (2015) 553–561 Oct.

[5] E.M. Abdel-Rahman, F. Turgut, K. Turkmen, R.A. Balogun, Falls in elderly hemodialysis patients, QJM 104 (10) (2011) 829–838 Oct.

[6] T.J. Arneson, S. Li, J. Liu, R.D. Kilpatrick, B.B. Newsome, W.L. St Peter, Trends in hip fracture rates in US hemodialysis patients, Am. J. Kidney Dis. 62 (4) (1993-2010) 747–754.

[7] A.M. Alem, D.J. Sherrard, D.L. Gillen, N.S. Weiss, S.A. Beresford, S.R. Heckbert, et al., Increased risk of hip fracture among patients with end-stage renal disease, Kidney Int. 58 (1) (2000) 396–399 Jul.

[8] M. Maravic, A. Ostertag, P.U. Torres, M. Cohen-Solal, Incidence and risk factors for hip fractures in dialysis patients, Osteoporos. Int. 25 (1) (2014) 159–165 Jan.

[9] J. Mares, K. Ohlidalova, S. Opatrna, J. Ferda, Determinants of prevalent vertebral fractures and progressive bone loss in long-term hemodialysis patients, J. Bone Miner. Metab. 27 (2) (2009) 217–223.

[10] Y. Maeno, M. Inaba, S. Okuno, K. Kohno, K. Maekawa, T. Yamakawa, et al., Significant association of fracture of the lumbar spine with mortality in female hemodialysis patients: a prospective observational study, Calcif. Tissue Int. 85 (4) (2009) 310–316 Oct.

[11] S.A. Jamal, C. Chase, Y.I. Goh, R. Richardson, G.A. Hawker, Bone density and heel ultrasound testing do not identify patients with dialysis-dependent renal failure who have had fractures, Am. J. Kidney Dis. 39 (4) (2002) 843–849. Apr.

[12] M. Inaba, S. Okuno, Y. Kumeda, T. Yamakawa, E. Ishimura, Y. Nishizawa, Increased incidence of vertebral fracture in older female hemodialyzed patients with type 2 diabetes mellitus, Calcif. Tissue Int. 76 (4) (2005) 256–260. Apr.

[13] M. Fusaro, G. Tripepi, M. Noale, A. D'Angelo, A. Naso, D. Miozzo, et al., Association of calcifediol levels with vertebral fractures, vascular calcifications and mortality, Kidney Res. Clin. Pract. 31 (2) (2012) A31.

[14] M. Atteritano, E. Di Mauro, V. Canale, A.M. Bruzzese, C.A. Ricciardi, V. Cernaro, et al., Higher serum sclerostin levels and insufficiency of vitamin D are strongly associated with vertebral fractures in hemodialysis patients: a case control study, Osteoporos. Int. 28 (2) (2017) 577–584 Feb.

[15] K. Atsumi, K. Kushida, K. Yamazaki, S. Shimizu, A. Ohmura, T. Inoue, Risk factors for vertebral fractures in renal osteodystrophy, Am. J. Kidney Dis. 33 (2) (1999) 287–293 Feb.

[16] R. Hasserius, M.K. Karlsson, B.E. Nilsson, I. Redlund-Johnell, O. Johnell, Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the Swedish cohort in the European Vertebral Osteoporosis Study, Osteoporos. Int. 14 (1) (2003) 61–68.

[17] C.M. Klotzbuecher, P.D. Ross, P.B. Landsman, T.A. Abbott, M. Berger, Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis, J. Bone Miner. Res. 15 (4) (2010) 721–739.

[18] U.A. Al-Sari, J.H. Tobias, E.M. Clark, Self-reported everyday physical activities in older people with osteoporotic vertebral fractures: a systematic review and meta-analysis, Osteoporos. Int. 29 (1) (2018) 19–29.

[19] D.M. Kado, M.H. Huang, A.S. Karlamangla, P. Cawthon, W. Katzman, T.A. Hillier, et al., Factors associated with kyphosis progression in older women: 15 years' experience in the study of osteoporotic fractures, J. Bone Miner. Res. 28 (1) (2013) 179–187.

[20] D.M. Kado, L. Lui, K.E. Ensrud, H.A. Fink, A.S. Karlamangla, Hyperkyphosis predicts mortality independent of vertebral osteoporosis in older women, Ann. Intern. Med. 150 (2009) 681–688.

[21] S. Katz, A. Ford, R.W. Moskowitz, B.A. Jackson, M.W. Jaffe, Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function, JAMA 185 (1963) 914–919.

[22] M.P. Lawton, E.M. Brody, Assessment of older people: self-maintaining and instrumental activities of daily living, Gerontologist 9 (3) (1969) 179–186.

[23] M.D. Miller, C.F. Paradis, P.R. Houck, S. Mazumdar, J.A. Stack, H.A. Rifai, et al., Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale, Psychiatry Res. 41 (3) (1992) 237–248.

[24] D. Podsiadlo, S. Richardson, The timed "Up & Go": a test of basic functional mobility for frail elderly persons, J. Am. Geriatr. Soc. 39 (2) (1991) 142–148 Feb.

[25] M.F. Folstein, L.N. Robins, J.E. Helzer, The mini-mental state examination, Arch. Gen. Psychiatry 40 (7) (1983) 812 Jul.

[26] J.A. Yesavage, J.I. Sheikh, 9/Geriatric depression scale (GDS), Clin. Gerontol. 5 (1–2) (1986) 165–173 Nov 18.

[27] L.P.P. Fried, C.M.M. Tangen, J. Walston, A.B.B. Newman, C. Hirsch, J. Gottdiener, et al., Frailty in older adults: evidence for a phenotype, J. Gerontol. Med. Sci. Am. 56 (3) (2001) 146–156 Mar.

[28] Electronic hand dynamometer, instructions for use [Internet], Available from: http://latodis-med.com/upload/pdf/dinamometru-digital-camry-eh-101.pdf.

[29] World Health Organization, WHO Global Report on Falls Prevention in Older Age. Community Health (Bristol) [Internet], (2007), p. 53. Available from: http://www.who.int/ageing/publications/Falls_prevention7March.pdf.

[30] H.K. Genant, C.Y. Wu, C. van Kuijk, M.C. Nevitt, Vertebral fracture assessment using a semiquantitative technique, J. Bone Miner. Res. 8 (9) (1993 Sep) 1137–1148.

[31] D.M. Kado, L. Christianson, L. Palermo, R. Smith-Bindman, S.R. Cummings, G.A. Greendale, Comparing a supine radiologic versus standing clinical measurement of kyphosis in older women: the fracture intervention trial, Spine (Phila Pa 1976) 31 (4) (2006) 463–467.

[32] C. McDaniels-Davidson, A. Davis, D. Wing, C. Macera, S.P. Lindsay, J.T. Schousboe, et al., Kyphosis and incident falls among community-dwelling older adults, Osteoporos. Int. 29 (1) (2018) 163–169.

[33] H.C. Van Der Jagt-willems, M.H. De Groot, J.P.C.M. Van Campen, C.J.C. Lamoth, W.F. Lems, Associations between vertebral fractures, increased thoracic kyphosis, a flexed posture and falls in older adults: a prospective cohort study, BMC Geriatr. 15 (34) (2015).

[34] M. Rodriguez-Garcia, C. Gomez-Alonso, M. Naves-Diaz, J.B. Diaz-Lopez, C. Diaz-Corte, J.B. Cannata-Andia, Vascular calcifications, vertebral fractures and mortality in haemodialysis patients, Nephrol. Dial. Transplant. 24 (1) (2009) 239–246 Jan.

[35] H. Chen, P. Lips, M.G. Vervloet, N.M. van Schoor, R.T. de Jongh, Association of renal function with bone mineral density and fracture risk in the Longitudinal Aging Study Amsterdam, Osteoporos. Int. 29 (9) (2018) 2129–2138.

[36] G. Coen, P. Ballanti, E. Bonucci, S. Calabria, S. Costantini, M. Ferrannini, et al., Renal osteodystrophy in predialysis and hemodialysis patients: comparison of histologic patterns and diagnostic predictivity of intact PTH, Nephron 91 (1) (2002) 103–111.

[37] C.-M. Zheng, J.-Q. Zheng, C.-C. Wu, C.-L. Lu, J.-F. Shyu, H. Yung-Ho, et al., Bone loss in chronic kidney disease: quantity or quality? Bone 87 (2016 Jun) 57–70.

[38] D.M. Kado, M. Huang, A.S. Karlamangla, E. Barrett-Connor, G.A. Greendale, Hyperkyphotic posture predicts mortality in older community-dwelling men and women: a prospective study, J. Am. Geriatr. Soc. 52 (2004) 1662–1667.

[39] W.B. Katzman, S.L. Harrison, H.A. Fink, L.M. Marshall, E. Orwoll, E. Barrett-connor, et al., Physical function in older men with hyperkyphosis, J. Gerontol. (2015) 635–640.

[40] S.D. Ryan, L.P. Fried, The impact of kyphosis on daily functioning, J. Am. Geriatr. Soc. 45 (1997) 1479–1486.

[41] J.R. Lunney, J. Lynn, C. Hogan, Profiles of older Medicare decedents, J. Am. Geriatr. Soc. 50 (6) (2002) 1108–1112.

[42] T. Roghani, M.K. Zavieh, F.D. Manshadi, N. King, W. Katzman, Age-related hyperkyphosis: update of its potential causes and clinical impacts-narrative review, Aging Clin. Exp. Res. 29 (4) (2018) 567–577.

[43] M.A. McAdams-DeMarco, A. Law, M.L. Salter, B. Boyarsky, L. Gimenez, B.G. Jaar, et al., Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis, J. Am. Geriatr. Soc. 61 (6) (2013) 896–901 Jun.