Chronic kidney disease and hip fracture-related mortality in older people in the UK

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Abstract

Background. Dialysis patients have increased hip fracture rates when compared to the general population of the same age and sex. There have been few studies of the association of earlier stages of chronic kidney disease (CKD) with hip fractures amongst older people in the general population. The aim of this study was to examine whether CKD at older ages is associated with hip-fracture-related mortality.

Methods. In a trial of health and social assessment of people aged 75 and over in the UK with baseline assessment between 1995 and 1998, there were 13 177 (87%) participants in 53 general practices who had a serum creatinine measured at baseline. Estimated glomerular filtration rate (eGFR) was derived from the modification of diet in renal disease formula (MDRD). Mortality follow-up using linkage to national mortality data was until the end of November 2005. We used propensity scores to adjust for potential confounders in Cox regression models.

Results. There were 84 hip-fracture-related deaths over a median follow-up of 7.25 years (IQR 3.79–8.77). Compared to eGFR 60 ml/min/1.73 m² and above, the age- and sex-adjusted hazard ratio (HR) for hip-fracture-related death was 1.06 (95% confidence interval: 0.71, 1.58) for eGFR 45–59 and 1.98 (1.12, 3.50) for eGFR < 45. In adjusted models, the HR for eGFR < 45 ml/min/1.73 m² compared to above was 1.81 (1.11, 2.96).

Conclusions. Amongst older people, an eGFR of <45 ml/min/1.73 m² is associated with an almost 2-fold increase in hip-fracture-related mortality.

Keywords: chronic kidney disease; estimated glomerular filtration rate; hip fracture; mortality; older people

Introduction

Hip fractures represent an important problem in older age, particularly so for women [1,2]. Risk factors for hip fracture in older age include diabetes, low weight, corticosteroid use, previous fractures, positive family history of hip fractures, self-reported health and physical activity [3]. The kidney is an important regulatory organ for the calcium–phosphate homeostasis in the body [4]. The irreversible loss of kidney function is associated with secondary hyperparathyroidism and the lack of synthesis of the active form of vitamin D with resulting metabolic bone disease [4,5]. It has been shown that patients on dialysis have approximately an overall four times higher risk of hip fracture than individuals in the general population of the same sex and age [6,7] that may be a result of metabolic bone disease, and also other mechanisms affecting bone strength such as avascular necroses. People with renal impairment may also have a higher risk of falling because of increased frailty, comorbidity and intense medication regimens. However, against expectations, the relative risk of fractures among dialysis patients is greatest at ages under 65 years [6].

The evidence for an association between hip fractures and kidney dysfunction in the general population is less certain, particularly at earlier stages of renal impairment and at older ages. In NHANES III (US cross-sectional national population-based survey), individuals with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² who were younger than 75 years of age were two to three times more likely to report a previous hip fracture than those without chronic kidney disease (CKD) [8]. In those aged 75 years and older, who are at highest risk for a hip fracture, there appeared to be no evidence of an association [8].

Thus there is considerable uncertainty about the effect of reduced renal function on hip fractures among older people in the general population. A large trial of health screening in people aged 75 years and above living in the community, from a representative sample of UK general practices [9–11], with baseline kidney function and mortality follow-up
enabled the investigation between decreases in eGFR and hip-fracture-related deaths.

Subjects and methods

Patient population

Full details of the trial have been reported previously [9,10]. In brief, the trial compared two methods of multidimensional assessment in people aged 75 and over registered in 106 general practices selected from the MRC General Practice Research Framework in England, Wales and Scotland, selected to be representative of the UK general practice standardized mortality ratios (SMRs) and Jarman deprivation score. All patients aged 75 or over registered with the practices were eligible and invited to participate unless they were resident in long-stay hospitals or nursing homes or had a terminal illness. Baseline assessments were conducted during 1995–1999. This paper focuses on the 53 practices in the ‘universal’ arm of the trial as here all patients were offered blood tests including serum creatinine. A total of 15,336 out of 20,934 (73.2%) subjects attended for baseline assessment in the universal arm; non-responders were older and more likely to be female [10,11].

Follow-up

All participants were flagged for mortality at the UK Government’s Office for National Statistics (ONS). ONS provided the date and coded cause of death using the International Classification of Diseases, 9th Revision (ICD-9) for deaths reported up until September 2002 and 10th Revision (ICD-10) after that date. Analyses are based on deaths up to the end of November 2005 for any reported fracturing of the hip. Hip fractures were taken as the following ICD codes on any part of the death certificate: neck of femur ICD9 = S72.1-9, S72.0; other areas of femur ICD9 = 820.9-8, ICD10 = S72.0; other areas of femur ICD9 = 821.0-3, ICD10 = S72.1-9.

All aspects of the original trial were approved by relevant local ethics committees.

Estimation of the glomerular filtration rate (eGFR)

A non-fasting blood sample was taken. Of the 45 local laboratories to which samples were sent, 37 used the modified Jaffe method for serum creatinine, 7 an enzymatic method and for 1 the method was unknown. The simple modification of diet in renal disease (MDRD) formula was used to calculate eGFR in ml/min/1.73 m² [12]. Subjects were divided into three eGFR groups: those with eGFR of 60 ml/min/1.73 m² or more, those with eGFR 45–59 ml/min/1.73 m² and those with <45 ml/min/1.73 m². Prior data suggested that the main effect, if present, was to be expected for those with eGFR <45 ml/min/1.73 m² [12]. A total of 13,177 out of 15,336 (86%) subjects who completed the in-depth assessment had an eGFR derivable. Missing data were due to there being no serum creatinine result. A significantly higher percentage of those with missing blood data died, though there was no difference in causes of death.

Confounders and propensity scores

Patient’s height, weight, waist circumference and blood pressure (the average of two sitting measures) were measured at baseline. Sociodemographic information, self-reported medical history, lifestyle and medication data were obtained by nurse interview. Socioeconomic status was classified by linking patient’s postcode to 1991 Census ward data from which the Carstairs deprivation score was derived. Diabetes was classified according to self-report of a medical diagnosis, use of anti-diabetic medication or the presence of a high random blood glucose measurement [13]. Cardiovascular disease (CVD) was based on history of either myocardial infarction or stroke. Drug use was coded into broad classes using the British National Formulary (BNF) chapter headings.

A priori confounders of the relation between CKD and hip-fracture-related mortality were age, sex, the use of anti-hypertensive drugs (thiazide diuretics, loop diuretics, other diuretics, beta or alpha blockers, ACE inhibitors, angiotensin receptor blockers and calcium channel blockers), drugs that may increase chance of a fall (hypnotic drugs, anti-psychotic, anti-depressive and Parkinson’s), drugs with effects on bone density (biphosphonates, oestrogen as hormone replacement therapy, vitamin D and calcium), self-reported alcohol drinking behaviour (never, ex and current drinker), the presence of diabetes, CVD and markers of a general frailty, such as a history of falls (less than 2 and 2 or more falls in the last 6 months), waist-to-hip ratio (WHR, in quintiles) and activities of daily living (ADL). The ADL were washing self, dressing self, cutting nails, cooking, shopping, doing light housework, walking 50 yards, going up and down stairs and steps—a person was coded as being partially dependent if more than two of these activities needed external help. Because haemoglobin (in quintiles) and phosphate serum levels (in quintiles) may be on the causal pathway between decrease in eGFR and hip fractures, we ran models with and without including these variables.

The number of strata needed for adjustment for above a priori confounders was very large in the setting of a low event rate. Conventional adjustments for all confounders would lead to an incorrectly specified regression model, as there were too few events to fill the many boxes specified by the number of strata (confounders). Hence, we used propensity scoring methods that allow us to estimate the fully adjusted effect of a binary exposure [14,15]. In the current setting we chose as binary cut-off a GFR <45 ml/min/1.73 m² because the main effect was noted for that category only. Therefore, the propensity score in this study was the conditional probability that an individual had a GFR <45 ml/min/1.73 m². This conditional probability was obtained for each individual by fitting a logistic regression model with outcome eGFR <45 ml/min/1.73 m² with above-mentioned list of confounding variables as predictors. All the potential confounding factors of interest were summarized through the propensity score [15]. Stratifying the analysis of the relation of exposure (eGFR < 45 ml/min/1.73 m²) with outcome for the propensity score is equivalent to adjusting for all the potential confounding factors that went into the estimation of the score,
while avoiding the problems of adjusting for a very large number of variables. This is because the distribution of confounding variables is on average the same among exposed and unexposed subjects who have an equal propensity score [15]. In the current analysis, only in the group with eGFR < 45 ml/min/1.73 m² did individuals have propensity score higher than 0.6. These 50 individuals were therefore excluded from the adjusted analyses because of the lack of a comparison group.

**Statistical analysis**

All data management and analyses were conducted using Stata version 9.2 [16]. Simple cross-tabulations of confounder exposure associations were carried with chi-square and Fisher’s exact tests where necessary. The analysis used the date of death on which the death certificate mentioned a fracture of the hip, with otherwise censoring dates being 30 November 2005 if still alive or the date of emigration for the few who left permanently (n = 8). Kaplan–Meier graphs and Cox’s proportional hazards modelling was used, with Nelson–Aalen graphs as a graphical check for the proportionality assumption in the Cox model, and Schoenfeld residual testing of the final models. Robust standard errors were used throughout to take account of the clustering effect within the 53 practices in the estimation of standard errors and P-values. We tested for interactions between eGFR and sex and found none. For propensity score modelling, eGFR was coded as a binary variable (45+ and <45 ml/min/1.73 m²).

Bootstrapping methods were used with 100 repetitions to account for the uncertainty associated with the estimation of propensity scores.

**Results**

**Study population at baseline**

There were 5111 men and 8056 women (61%) who had available serum creatinine measurements to derive MDRD eGFR at inclusion into the trial [12]. The median age of included subjects was 80.3 years (inter-quartile range: 77.2–84.1 years). Table 1 presents the distribution of key covariates stratified by sex and eGFR category. eGFR was lower at higher ages and among people with prevalent CVD and diabetes (in females only). In line with cardiovascular morbidity, the use of aspirin, statins and hypertensive drugs increased across decreasing eGFR categories. There was a borderline significant association with prevalent smoking in the opposite direction with current smokers having a slightly higher eGFR than non-smokers. Those who reported regular current alcohol intake tended to have higher eGFR than those who did not report any alcohol consumption. Haemoglobin values decreased with decreasing eGFR, particularly in those with eGFR<45 ml/min/1.73 m², and participants with lower eGFR tended to perform less exercise and were more dependent on other individuals for their activities of daily living. Those with an eGFR <45 ml/min/1.73 m² were more likely to report more than two falls in the preceding 6 months as well as the use of drugs associated with a propensity to fall. With decreasing eGFR categories, median WHRs and phosphate levels increased in both men and women, with no obvious change in the pattern of drugs affecting bone metabolism.

**Hip-fracture-related mortality during follow-up**

Over a median follow-up of 7.25 years (IQR 3.79–8.77), 84 hip-fracture-related deaths occurred out of a total of 7633 deaths. The crude incidence of hip-fracture-related mortality was higher for those with eGFR < 45 ml/min/1.73 m² when compared to higher eGFR bands (Figure 1). The hazard for hip-fracture-related mortality almost doubled for those with eGFR < 45 ml/min/1.73 m² when compared to those with 60 ml/min/1.73 m² and above in age- and sex-adjusted analysis (Table 2). When adjusting the analyses for confounding variables including anaemia, other pre-existing comorbidity and factors associated with bone strength/disease (e.g. phosphate levels at baseline), the hazard of hip-fracture-related mortality was ~80% higher for those with eGFR < 45 ml/min/1.73 m² when compared to those with eGFR above (Table 2). Omission of haemoglobin and phosphate levels from the propensity score model led to a similar result with a hazard ratio (HR) of 1.87 (1.15–3.05) for the effect of eGFR < 45 ml/min/1.73 m². Based on the fully adjusted analyses (Table 2), 44.7% of hip-fracture-related deaths amongst older people with eGFR < 45 ml/min/1.73 m² appear to be attributable to the kidney dysfunction itself.

**Discussion**

We found an independent association between reduced eGFR and hip-fracture-related mortality with a doubling of risk for those with eGFR < 45 ml/min/1.73 m². Even after adjusting for confounding factors, it appears that amongst those with eGFR < 45 ml/min/1.73 m², a substantive proportion of hip-fracture-related deaths appeared to be related to the kidney dysfunction itself.

There are a number of limitations in the interpretation of our results. Our results are based only on mortality and not on the incidence of hip fracture. It is likely that hip fracture mortality is underestimated because of other associated causes of death. Impaired renal function is related to all-cause and cardiovascular mortality, and the fully adjusted point estimates for the HR associated with eGFR < 45 ml/min/1.73 m² for all-cause mortality were 1.37 for women and 1.69 for men in this cohort. On the other hand, because hip fractures account for 50% of subsequent death of all acute orthopaedic hospitalizations [17], hip-fracture-related mortality may still be a good measure of hip fracture incidence. In line with this, our study found a crude incidence of hip-fracture-related death of 1 per 1000 person years, which is just about half of the expected hip fracture incidence for that age group.

We did not have a direct measure of the true kidney function and used eGFR based on the MDRD formula, which lacks validation in older people. We had only a single measurement of creatinine that was done in several laboratories. However, previous studies have reported good validity of
Table 1. Key covariates by eGFR category (in ml/min/1.73 m²) and gender

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men eGFR band</th>
<th>Women eGFR band</th>
<th>χ² P-value</th>
<th>Men eGFR band</th>
<th>Women eGFR band</th>
<th>χ² P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60+</td>
<td>45–59</td>
<td>&lt;45</td>
<td></td>
<td>60+</td>
<td>45–59</td>
</tr>
<tr>
<td>Number at baseline</td>
<td>2889</td>
<td>1636</td>
<td>586</td>
<td>&lt;0.001*</td>
<td>2884</td>
<td>3419</td>
</tr>
<tr>
<td>Median age in years (inter-quartile range)</td>
<td>78.8 (76.6–82.1)</td>
<td>80.3 (77.1–84.1)</td>
<td>81.3 (78.3–85.3)</td>
<td>&lt;0.001</td>
<td>79.5 (77.0–83.0)</td>
<td>80.6 (77.3–84.4)</td>
</tr>
<tr>
<td>CVD at baseline</td>
<td>515 (18%)</td>
<td>391 (24%)</td>
<td>207 (35%)</td>
<td>&lt;0.001</td>
<td>327 (11%)</td>
<td>482 (14%)</td>
</tr>
<tr>
<td>Median haemoglobin (inter-quartile range)</td>
<td>14.2 (13.3–14.9)</td>
<td>14 (13.1–14.9)</td>
<td>13.2 (12.1–14.3)</td>
<td>&lt;0.001</td>
<td>13.1 (12.4–13.9)</td>
<td>13.1 (12.3–13.9)</td>
</tr>
<tr>
<td>Smoking</td>
<td>536</td>
<td>303</td>
<td>105</td>
<td>0.187</td>
<td>1419</td>
<td>1804</td>
</tr>
<tr>
<td>Never</td>
<td>1902</td>
<td>1112</td>
<td>407</td>
<td></td>
<td>298 (10%)</td>
<td>303 (9%)</td>
</tr>
<tr>
<td>Ex</td>
<td>454 (16%)</td>
<td>218 (13%)</td>
<td>74 (13%)</td>
<td></td>
<td>521 (18%)</td>
<td>358 (22%)</td>
</tr>
<tr>
<td>Current</td>
<td>536</td>
<td>303</td>
<td>105</td>
<td></td>
<td>1419</td>
<td>1804</td>
</tr>
<tr>
<td>Diabetes</td>
<td>862 (30%)</td>
<td>694 (42%)</td>
<td>342 (58%)</td>
<td>&lt;0.001</td>
<td>1068 (37%)</td>
<td>1502 (44%)</td>
</tr>
<tr>
<td>Any anti-hypertensives</td>
<td>190 (7%)</td>
<td>120 (7%)</td>
<td>55 (9%)</td>
<td>0.146</td>
<td>215 (7%)</td>
<td>287 (8%)</td>
</tr>
<tr>
<td>More than two falls at home in last 6 months</td>
<td>190 (7%)</td>
<td>120 (7%)</td>
<td>55 (9%)</td>
<td>0.146</td>
<td>215 (7%)</td>
<td>287 (8%)</td>
</tr>
<tr>
<td>ADL partially dependant (2+)</td>
<td>521 (18%)</td>
<td>358 (22%)</td>
<td>203 (35%)</td>
<td>&lt;0.001</td>
<td>848 (29%)</td>
<td>1137 (33%)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>199</td>
<td>130</td>
<td>58</td>
<td>0.043</td>
<td>483</td>
<td>668</td>
</tr>
<tr>
<td>Never</td>
<td>165</td>
<td>111</td>
<td>46</td>
<td></td>
<td>137</td>
<td>183</td>
</tr>
<tr>
<td>Ex</td>
<td>2469 (85%)</td>
<td>1355 (83%)</td>
<td>468 (80%)</td>
<td></td>
<td>2176 (75%)</td>
<td>2472 (72%)</td>
</tr>
<tr>
<td>Current</td>
<td>2398</td>
<td>1313</td>
<td>407</td>
<td>&lt;0.001</td>
<td>2259</td>
<td>2631</td>
</tr>
<tr>
<td>Very/Fairly</td>
<td>482 (17%)</td>
<td>315 (19%)</td>
<td>175 (30%)</td>
<td></td>
<td>595 (21%)</td>
<td>765 (22%)</td>
</tr>
<tr>
<td>Not very/not at all</td>
<td>0.935 (0.90–0.98)</td>
<td>0.939 (0.90–0.98)</td>
<td>0.941 (0.90–0.98)</td>
<td>0.046*</td>
<td>0.837 (0.80–0.84)</td>
<td>0.835 (0.80–0.88)</td>
</tr>
<tr>
<td>Median WHR (inter-quartile range)</td>
<td>1 (0.89–1.12)</td>
<td>1.01 (0.91–1.13)</td>
<td>1.08 (0.94–1.19)</td>
<td>&lt;0.001*</td>
<td>1.12 (1.02–1.25)</td>
<td>1.12 (1.01–1.23)</td>
</tr>
<tr>
<td>Median phosphate (inter-quartile range)</td>
<td>296 (10%)</td>
<td>172 (11%)</td>
<td>92 (16%)</td>
<td>0.002</td>
<td>512 (18%)</td>
<td>606 (18%)</td>
</tr>
<tr>
<td>All falls-related drugs</td>
<td>21 (0.7%)</td>
<td>7 (0.4%)</td>
<td>5 (0.9%)</td>
<td>0.440</td>
<td>105 (3.6%)</td>
<td>119 (3.5%)</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, numbers and percentage breakdowns of columns are displayed.
*Chi-square P-values were produced by categorizing variables into quintiles.
Chronic kidney disease and hip fracture mortality

eGFR cut-offs below 60 ml/min/1.73 m² irrespective of the type of creatinine assay used [18].

The use of propensity scores enabled us to adjust for a very large range of confounding variables [14]. Conventional adjustments would have led to a misspecified model with too many strata and violations of proportionality. We excluded from the comparison group those who, based on their propensity score, were likely to have kidney disease as otherwise the effect of kidney disease would have been over-estimated due to the lack of an adequate comparison with an equal set of confounders. The findings highlight that those with severe renal impairment tend to be a select population with a distinct pattern of comorbidity and associated medications. We were not able to assess the effect of potential mediators of the relationship between kidney function and bone disease, such as homocysteine, vitamin D and PTH values, or direct measurements of bone loss or bone biopsies. Although we adjusted for a wide range of confounding variables, we cannot exclude that there is unmeasured confounding.

The mechanisms put forward for the association between renal impairment and hip fractures observed in younger populations include three mechanisms: the direct effects of kidney disease on the vitamin D, phosphate and bone turnover [19–21], kidney disease being a marker for increased comorbidity and frailty with falls [6,8,19–23] and the association of kidney disease with higher homocysteine levels [24] that may be associated with bone strength [25,26]. Serum PTH rises at eGFR < 60 ml/min/1.73 m², whereas serum phosphate does not rise substantially until an eGFR < 30 ml/min/1.73 m² [27,28]. Small rises in PTH at eGFR < 60 ml/min/1.73 m² do not appear to be of major importance—the crude association of reduced bone mineral density with eGFR < 60 ml/min/1.73 m² in NHANES III was fully explained by age, sex and weight [29]. A recent cohort study of community-dwelling adults aged 65 years found only a weak crude association between eGFR < 60 ml/min/1.73 m² and incident hip fractures that was attenuated when age was taken into account [22]. We found no increased risk at eGFR 45–59 ml/min/1.73 m² that is largest group of people with moderate CKD [11]. However, in this study there were strong associations for eGFR < 45 ml/min/1.73 m². The association persisted despite adjustments for medication and comorbidities associated with frailty and falls. This fits with previous findings of a dose–response association in a small case–cohort study in women aged 65 years or more [23]. In our study, anaemia and baseline phosphate levels were insufficient to explain

**Table 2.** Hazard ratios [(HR) age and sex adjusted and propensity score adjusted] for the effect of estimated glomerular filtration rate on hip fracture on death certificate

<table>
<thead>
<tr>
<th>eGFR (ml/min/1.73 m²)</th>
<th>Hip-fracture-related deaths</th>
<th>( n/N )</th>
<th>Person years</th>
<th>HR (95% CI)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted age and sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60+</td>
<td></td>
<td>28/5783</td>
<td>38 635</td>
<td>1 (ref)</td>
<td>–</td>
</tr>
<tr>
<td>45–59</td>
<td></td>
<td>31/5055</td>
<td>32 797</td>
<td>1.06 (0.71–1.58)</td>
<td>0.768</td>
</tr>
<tr>
<td>&lt;45</td>
<td></td>
<td>25/2339</td>
<td>12 685</td>
<td>1.98 (1.12–3.50)</td>
<td>0.019</td>
</tr>
<tr>
<td>Adjusted for propensity scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45+</td>
<td></td>
<td>59/10 827</td>
<td>71 368</td>
<td>1 (ref)</td>
<td>–</td>
</tr>
<tr>
<td>&lt;45</td>
<td></td>
<td>24/2300</td>
<td>12 522</td>
<td>1.81 (1.11–2.96)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Adjusting for propensity scores in 13 categories, which balance out distributions of age, sex, anti-hypertensives [thiazide diuretics, loop diuretics, other diuretics, beta or alpha blockers (combined), ACE inhibitors, angiotensin receptor blockers, calcium channel blockers and others], drugs associated with a propensity to fall (hypnotic drugs, anti-psychotic, anti-depressive, Parkinson’s), diabetes, cardiovascular disease, haemoglobin (quintiles), fall history, smoking, exercise (not very active/not at all versus fairly active), use of alcohol, waist-to-hip ratio (quintiles), blood phosphate levels (quintiles), drugs affecting bone structure (biophosphonates, oestrogen, phosphate binders, vitamin D, calcium), activity of daily living (ADL) partial scores. Analyses are excluding 50 observations with PS above 0.6 (<45 eGFR).
the association between eGFR < 45 ml/min/1.73 m² and hip-fracture-related mortality.

Despite its limitations, this study implies that there may be a substantive portion of hip-fracture-related deaths related to kidney dysfunction. Many of the important mediators in kidney disease that were discussed above are potentially treatable (e.g., prevention of falls, aggressive inpatient management of fracture) and deserve more intensive study in older patients.

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Conflict of interest statement. None declared.

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