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Increased hip fracture and mortality in chronic kidney disease individuals: The importance of competing risks

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ABSTRACT

Background: Many studies have shown a correlation between chronic kidney disease (CKD) and fracture. However, increased mortality in CKD patients is a competing risk scenario not accounted for in previous studies. Our aim was to investigate the true impact of CKD on hip fracture after accounting for a competing risk with death.
Methods: We conducted a population-based cohort study to determine the impact of CKD on hip fractures in individuals aged ≥50 years old registered in the SIDIAP^{Q} database (representative of 1.9 million people in Catalonia, Spain). Cox regression was used to estimate hazard ratio (HR) for death and hip fracture according to CKD status. A competing risk (Fine and Gray) model was fitted to estimate sub-HR for hip fracture in CKD or CKD-free patients accounting for differential mortality.
Results: A total of 873,073 (32,934 (3.8%) CKD) patients were observed for 3 years. During follow-up, 4,823 (14.6%) CKD and 36,328 (4.3%) CKD-free participants died (HR, 1.83 [95% CI, 1.78–1.89]), whilst 522 (1.59%) and 6,292 (0.75%) sustained hip fractures, respectively. Adjusted Cox models showed a significantly increased risk of hip fractures for the CKD group (HR, 1.16 [1.06–1.27]), but this association was attenuated in competing risk models accounting for mortality (SHR, 1.14 [1.03–1.27]).
Conclusions: Both death and hip fracture rates are increased (by 83% and 16%, respectively) in CKD patients. However, the association between CKD and hip fractures is attenuated when an excess of mortality is taken into account. A competing risk with death must be considered in future analyses of association between CKD and any health outcomes.

Introduction

Chronic kidney disease (CKD) affects 5–10% of the world population [1] and is associated with excess mortality [2]. CKD-related mineral bone disease is characterized by alterations in bone turnover, mineralization and volume that result in an increased bone fragility and subsequently in a higher risk of fracture [3]. Similarly, osteoporosis is defined as a skeletal disorder characterized by compromised bone strength that leads to an increased risk of fracture [4]. Fractures are the main clinical manifestation of osteoporosis, with an incidence that is expected to increase [5] and with a substantial medical and economic burden [6].

As care for CKD has improved, the affected population has continued aging, and osteoporosis and fractures have become a growing concern among nephrologists. Besides renal osteodystrophy, a classical syndrome that has drawn the attention of our community for years [7,8], there is an increasing interest nowadays in the impact of subtle kidney–bone axis alterations, which lead to higher morbidity and mortality in these patients with the associated impact on cost [9,10]. Among dialysis patients, a four-fold higher prevalence of fractures compared to the general population has been observed [11–14]. This association is not only found in dialysis patients but also in kidney transplant [13,15], and in early stages of CKD [16–27], where patients may already present mineral metabolism alterations including secondary hyperparathyroidism and vitamin D deficiency. However, the data are conflicting, with a number of reports showing no increased fracture risk in CKD patients [28,29], in part due to differences in the characteristics of the population studied, fracture sites assessed and definitions of CKD used. In addition, the study participants in many previous studies were recruited

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in specialized care settings, making them non-representative of the entire CKD population living in the community.

More importantly, to our knowledge, no previous studies have accounted for a competing risk with known increased mortality among CKD patients compared to the general population when studying the association between CKD and fracture risk. We hypothesize that failing to account for differences in mortality using available analytical methods has led to an overestimation of the excess risk of hip fracture in CKD patients, as it has been described in other research areas [30].

Therefore, our aim was to study the excess risk of hip fracture associated with CKD in the community taking into account the excess risk of mortality in CKD patients, and to compare these results to those obtained using the widely popular proportional hazards Cox regression methods, which fail to account for a competing risk with death.

Materials and methods

Source of data and study design

We carried out a population-based retrospective cohort study using data from the SIDIAP^{Q} (Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària) database. SIDIAP^{Q} contains the primary care computerized medical records of more than 1,300 general practitioners (GPs) in Catalonia (North-East Spain), with information on a representative 30% of the population (>2 million people) [31]. It comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) in electronic medical records, sociodemographic information, pharmacy invoicing data, as well as referrals to imaging, secondary care and their main outcomes [32]. Only GPs who achieve coding quality standards can contribute to the SIDIAP^{Q} database [33]. Health professionals gather the information recorded in SIDIAP^{Q} using ICD-10 codes, and structured forms designed for the standardized collection of variables relevant for primary health care, including lifestyle risk factors (smoking and alcohol drinking) and anthropometric measurements (height, weight and body mass index), among others.

SIDIAP^{Q} is further linked to the official hospital inpatient records database (CMBD-AH for its acronym in Catalan language) to improve data completeness, and it has been shown to compile valid and representative information on a number of health outcomes compared to national health survey data [34] as well as to classic cohort studies [35,36].

Date of death is registered in the SIDIAP database as provided by the National Mortality Register.

Study participants

We included all men and women aged ≥50 years old registered in the SIDIAP^{Q} database on 1/1/2007.

Exposure: CKD

Participants were screened for CKD using a validated list of ICD-10 codes for the identification of common co-morbid conditions in administrative datasets [37]. The following codes were used to identify CKD patients: I12.0, I13.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N18, N18.0, N18.8, N18.9, N19, N25.0, Z49.0, Z49.1, Z49.2, Z94.0 and Z99.2. There is an agreed protocol for the identification and management of patients with CKD in primary and secondary care [38]. Based on this, CKD is defined as estimated glomerular filtration rate (eGFR) by modified-diet renal disease 4 (MDRD-4) below 60 ml/min/m^2.

Outcome: hip fractures

Incident hip fractures in the study period (1/1/2007 to 31/12/2009) were ascertained within both primary care and hospital episodes data using a published list of ICD-10 codes for hip fractures. These fracture codes have been validated in SIDIAP^{Q} primary care records compared to prospective cohort data as a reference, and shown to be highly specific (>90%) but less sensitive (68% for hip fractures) [39]. Hospital admission records were used to identify fractures with the aim of minimizing misclassification.

Statistical analyses

Hip fracture incidence and mortality rates in the CKD and CKD-free population, and 95% confidence intervals (95% CI), were calculated assuming a Poisson distribution. Hazard ratio (HR) and 95% CI for mortality risk according to CKD status was estimated using proportional hazards Cox regression.

In a first set of analyses on the association between CKD and hip fracture risk, Cox regression models were fitted to estimate hazard ratio (HR) and 95% CI according to CKD status without accounting for competing risk with death. Secondly, Fine and Gray models [40] were fitted to estimate sub-hazard ratio (SHR) and 95% CI on the association between CKD and hip fracture risk accounting for a competing risk with death. CKD status was introduced in all these models as a time-varying covariate when patients did not have a prevalent diagnosis of CKD (at 1/1/2007) but were newly diagnosed with CKD during follow-up (and before fracturing).

All the previously described models were adjusted for the following list of a priori defined potential confounders: age, gender, body mass index, smoking, alcohol intake, use of oral steroids (>90 days of prednisolone 5 mg/d or equivalent) and history of type 2 diabetes mellitus.

We also defined a priori interactions with age (≤65 versus >65 years old), gender and type 2 diabetes mellitus. These were tested for by introducing multiplicative terms in the models, and stratified results were reported when the interactions were significant. Kaplan–Meier estimates of age-adjusted cumulative fracture risk stratified by CKD status were plotted.

All these analyses were carried out using Stata SE for Mac version 12.0.

Results

We identified 873,073 eligible people aged 50 years or older registered in SIDIAP^{Q} on 01/01/2007. Of these, 15,062 patients had CKD by 01/01/2007, and 17,872 patients developed CKD during the study time frame (until 12/31/2009), for a total of 32,934 CKD patients (3.77%). CKD and CKD-free patients were followed up for a similar median of 2.997 (interquartile range 0.01) years. Two percent of the individuals included in the database were lost to follow-up.

When compared to the CKD-free population in SIDIAP, CKD patients were older, more overweight/obese, and more likely to be male, steroid users, and type 2 diabetic. Baseline characteristics for the study population stratified by CKD status are detailed in Table 1.

During the study period, 41,151 (4.7%) individuals died. Mortality was higher for CKD patients (4,823; 14.6%) compared to CKD-free participants (36,328; 4.3%). In a Cox model analysis, fully adjusted HR for mortality in CKD patients was 1.83 [95% CI, 1.78–1.89]. A significant and clinically relevant interaction with age was detected (p value for interaction <0.001): adjusted HR for the association between CKD and death in people ≤65 years was 3.35 [2.80–4.01], compared to a HR of 1.81 [1.76–1.87] in those aged 65 years or older. Detailed results for the association between CKD and death are reported in Table 2.