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Fracture status in middle-aged individuals with early CKD: cross-sectional analysis of the CARTaGENE survey

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Abstract

Summary Whether early chronic kidney disease (CKD) is associated with fracture in middle-aged adults is unclear. In a cross-sectional analysis of the CARTaGENE survey, we observed that early CKD was not associated with increased fracture, did not modify the association between calcaneal QUS and fracture, but modified the association between clinical, pharmacological parameters and fracture.

Introduction The association between advanced CKD and increased fracture risk is well described. However, whether early CKD is associated with increased fractures, especially in middle-aged adults, is unclear. We aimed to assess if early CKD is associated with increased fracture status and whether early CKD status modifies the association between calcaneal quantitative ultrasound parameters, clinical, pharmacological parameters, and fractures.

Methods Cross-sectional analysis of CARTaGENE, a population-based survey of 40- to 69-year-old individuals. Individuals with CKD (stage 2, estimated glomerular filtration rate [eGFR] 60–89 ml/min/1.73 m^2; stage 3, eGFR 30–59) were compared to non-CKD individuals (eGFR > 90). Fracture status (excluding face, toe, hand, and patella) was identified through a questionnaire at baseline. Calcaneal quantitative ultrasound (QUS) was measured in each participant.

Results A total of 17,608 individuals (656 CKD stage 3; 8227 stage 2; 8725 non-CKD) were included. CKD stage 2 and 3 individuals (mean eGFR 78 and 53 ml/min/1.73 m^2) were older and had more diabetes, cardiovascular disease, and hypertension. Fracture status prevalence was 14.9% in CKD stage 3, 10.8% in CKD stage 2, and 9.0% in non-CKD individuals. Fracture status prevalence was similar between CKD and non-CKD individuals when stratified by age or after adjustment for demographic and clinical parameters. QUS stiffness index was associated with fracture status in both CKD stage 3 (standardized odds ratio [sOR] = 1.525 [1.200 to 1.939] per 1 SD decrease), stage 2 (sOR = 1.415 [1.310 to 1.530]), and non-CKD individuals (sOR = 1.477 [1.361 to 1.602]). The associations between blood pressure, antihypertensive, and fracture status followed a U-shape throughout the progression of CKD.

Conclusions CKD stage 3 was not associated with an increase in fracture status. QUS parameters were similarly associated with fracture status in patients with and without CKD.

Keywords CARTaGENE · Chronic kidney disease · Fracture

Introduction

Chronic kidney disease–mineral and bone disorder (CKD-MBD) is a major health issue leading to increased fractures and vascular calcification, which are responsible for heightened morbidity and mortality in CKD populations [1–4]. The association between end-stage renal disease (ESRD) and increased risk of fracture has now been well recognized [5–7]. Indeed, fracture incidence at various anatomical sites has been reported to be increased in ESRD [5, 8], while recent Kidney Disease: Improving Global Outcomes guidelines now suggest the use of bone mineral density (BMD) to identify patients at risk of fracture in dialysis populations [9, 10].

In contrast to ERSD patients, the association between mild to moderate CKD (stages 2 and 3) and increased risk of fracture is controversial. While some studies have reported an increased risk of fracture in milder stages of CKD [3, 11–14], others failed to report such an increase after

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adjustment for age and comorbidities [15–17]. Furthermore, these studies have often assessed hip fracture only and have mainly studied old and morbid populations. Similarly, risk factors for fracture in mild to moderate CKD populations have not been well defined as a recent meta-analysis highlighted the lack of large studies to address this issue [10]. Since even a mild reduction of kidney function may alter bone metabolism, it is, therefore, possible that risk factors for fracture are different between mild to moderate CKD and non-CKD population.

Considering the uncertainties about fractures in mild to moderate CKD, we used a large population-based survey (CARTaGENE) to assess the effect of CKD on the prevalence and risk factors for fracture. Our primary objective was to compare fracture status between CKD and non-CKD individuals. Secondary objectives were to compare the association between calcaneal quantitative ultrasound (QUS); clinical, biochemical, pharmacological parameters; and fracture status in CKD vs non-CKD individuals.

Material and methods

Study design and population

We conducted a cross-sectional analysis of CARTaGENE, a large population-based health survey of 40- to 69-year-old individuals from the province of Quebec (Canada). This survey aimed to study the relation between genomics and prevalence of chronic diseases. Details on CARTaGENE recruitment have been previously published [18–21]. Briefly, using governmental health insurance database, participants were randomly selected between 2009 and 2010 to represent 1% of the Quebec population between 40 and 69 years of age. For this study, all individuals with available data on calcaneal QUS, serum creatinine, and fracture status were included unless they were under anti-resorptive or anabolic bone therapies, were in CKD stages 4–5 [estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2], on hemodialysis, or kidney transplanted. CKD was defined as an eGFR between 30 and 59 ml/min/1.73 m^2 for stage 3 and eGFR between 60 and 89 ml/min/1.73 m^2 for stage 2 according to the KDIGO classification [22]. Non-CKD group was defined as eGFR above 90 ml/min/1.73 m^2. All participants signed informed consent. This study adhered to Helsinki Declaration and has been approved by appropriate ethics committees.

Data collection

Participants in the CARTaGENE survey answered a validated health and lifestyle questionnaire including fracture history at the baseline visit. Medication list was collected for each participant with a nurse-filled questionnaire. QUS measurement and blood samples were then collected and eGFR was calculated from IDMS-calibrated creatinine serum measurement using the CKD-EPI equation [23]. Physical activity levels were collected at baseline using a standardized questionnaire and expressed as metabolic equivalents (METs)-hour per week.

Fracture and QUS assessment

Fractures that occurred after the age of 40 were identified through a questionnaire at baseline. All fractures were included except for toes, hand, face, and patella fractures. Major osteoporotic fracture status was defined as the occurrence after the age of 40 of a hip, vertebral, forearm, or humerus fracture. Calcaneal QUS was performed at baseline (Lunar Achilles Express, GE Healthcare, Madison, WI) and measured the speed of a wave sound (speed of sound; SOS) and its attenuation (broadband ultrasound attenuation, BUA) across the individual's heel. These two parameters were then combined to generate a stiffness index [24].

Statistical analysis

SAS 9.4 (SAS Institute, Cary, NC, USA) was used for data analysis. Values with $p < 0.05$ were considered significant. Baseline characteristics for CKD and non-CKD individuals were compared using an ANOVA or a Fisher test. Fracture status was compared between CKD stage 3, stage 2, and non-CKD using a global Fisher test and was then stratified for age categories (40–50, 50–60, 60–70). Associations between kidney function (either expressed as categorical [CKD status] or continuous [eGFR] variables) and fracture status were assessed with logistic regression models adjusted for age, gender, ethnicity, cardiovascular disease, smoking, diabetes, physical activity levels, statin, vitamin D supplementation, calcium supplementation, hormonal replacement therapy, and benzodiazepine and antihypertensive usage. The association of QUS parameters (stiffness index, SOS, BUA) with fracture in each CKD group was evaluated in unadjusted and adjusted (for age, sex, and ethnicity) logistic regression models including an interaction term between the QUS parameters and CKD stage (expressed as a categorical variable). Additional analyses were conducted by replacing the QUS-CKD stage interaction with an interaction term between each QUS parameter and eGFR levels. The modification effect of CKD on the association between clinical, pharmacological, and biochemical parameters and fracture status was similarly analyzed. Interaction terms with a p value under 0.1 were considered statistically significant.

Results

Population characteristics

Among the 20,004 participants recruited in CARTaGENE, 17,608 were included in this study (Fig. 1). A total of 656 individuals were classified as stage 3 CKD, 8227 as stage 2 CKD, and 8725 as non-CKD. As reported in Table 1, stage 2 and 3 CKD individuals (mean eGFR of 78 ± 8 and 53 ± 6 ml/min/1.73 m^2 respectively) were older and had a higher prevalence of diabetes, cardiovascular disease, hypertension, and higher levels of uric acid and total cholesterol than non-CKD individuals (mean eGFR 100 ± 7 ml/min/1.73 m^2).

Association between CKD and fracture status

A total of 1764 (10.0%) individuals experienced at least one fracture after 40 years in CARTaGENE. Anatomical sites of prevalent fractures were as follows: 24 hip (1.4%), 21 pelvis (1.2%), 102 vertebra (5.8%), 219 ribs (12.4%), 690 upper limb (39.1%), and 870 lower limb (49.3%). As displayed in Table 1, fracture prevalence was 14.9% in stage 3 CKD, 10.8% in stage 2 CKD, and 9.0% in non-CKD ($p < 0.001$). When stratified for age, there was no significant difference in fracture prevalence between CKD and non-CKD groups (Fig. 2). In logistic univariate regression models, CKD status and eGFR were both associated with fracture status (Fig. 3). However, when adjusted for age, demographic and clinical parameters, neither CKD status nor eGFR were associated with fracture status. Similar results were obtained when major osteoporotic fracture status was used as an outcome. The association between CKD stage 3 and fracture status was similar in men and women (p for interaction 0.226). In contrast, gender modified the association between CKD stage 2 and fracture status (p for interaction 0.03; OR = 0.816 [0.701 to 0.949] in men; OR = 1.025 [0.886 to 1.187] in women).

Association between QUS and fracture status in CKD and non-CKD individuals

In univariate analysis, the QUS stiffness index was associated with fracture status in both CKD stage 2, CKD stage 3, and non-CKD groups (Fig. 4). The multiplicative interaction term between the stiffness index and either CKD status or eGFR was not statistically significant. In multivariate models adjusted for age, gender, and ethnicity, the stiffness index remained associated with fracture status in CKD and non-CKD (Fig. 4). Similarly, the multiplicative modification effect of either CKD status or eGFR on the association between the stiffness index and fracture status was not statistically significant in these models. As displayed in Fig. 4, similar results were obtained for SOS and BUA. Further adjustment for physical activity levels did not influence the association between the stiffness index and fracture status in each CKD group (standardized OR [sOR] = 1.528 [1.202 to 1.942] in CKD stage 3; sOR = 1.418 [1.312 to 1.532] in CKD stage 2; sOR = 1.478 [1.363 to 1.604] in non-CKD).

Factors associated with fracture status in CKD and non-CKD individuals

The association between clinical, biochemical, pharmacological parameters and fracture status was assessed in multivariate models stratified for CKD status and adjusted for age and gender (Table 2). Systolic blood pressure was associated with increased fracture status in non-CKD and decreased fracture status in stage 2 CKD but not associated with fracture in stage 3 CKD. Its interaction term was significant with both CKD status and eGFR levels. Diastolic blood pressure was significantly associated with increased fracture in non-CKD and stage 3 CKD individuals. Its interaction term was significant with CKD status but not with eGFR levels. Similar association point estimates were obtained when the analysis was restricted to individuals without antihypertensive usage. While

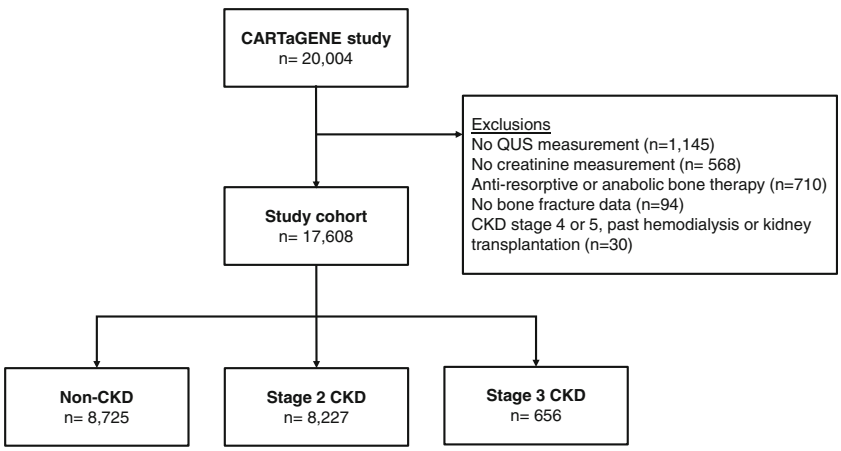

Fig. 1 Study flowchart. The chart presents the individuals' inclusion-exclusion and classification by CKD status. Stage 2 CKD was defined as eGFR between 60 and 89 ml/min/1.73 m^2 and stage 3 CKD as eGFR between 30 and 59 ml/min/1.73 m^2 as computed by CKD-EPI. The sum of the exclusion reasons is superior to the number of excluded patients because some patients were excluded for more than one reason. QUS, quantitative ultrasound; CKD, chronic kidney disease

Table 1 Population characteristics

	Non-CKD ($n = 8725$)	CKD stage 2 ($n = 8227$)	CKD stage 3 ($n = 656$)	p value
Demography				
Age (years)	52 ± 7	56 ± 8	60 ± 7	< 0.001
Sex (male)	48.4	51.3	49.8	0.005
Body mass index	27 ± 5	28 ± 5	29 ± 6	< 0.001
Ethnicity				< 0.001
White	87.4	91.7	87.8	
Black	1.7	2.0	4.3	
Hispanic	2.8	1.7	1.1	
Other	8.1	4.6	4.8	
Comorbidities				
Diabetes mellitus	8.5	8.1	19.8	< 0.001
Cardiovascular disease	4.5	7.0	13.9	< 0.001
Hypertension	24.0	29.9	53.2	< 0.001
Current smoking	5.2	3.9	3.5	< 0.001
Physical activity (METs-hour per week)	52 ± 49	52 ± 48	47 ± 44	0.04
Biochemistry				
eGFR (ml/min/1.73 m^2)	100 ± 7	78 ± 8	53 ± 6	< 0.001
Uric acid (μmol/l)	288 ± 76	314 ± 78	365 ± 90	< 0.001
Total cholesterol (mmol/l)	5.1 ± 1.0	5.1 ± 1.0	5.0 ± 1.2	< 0.001
Bone parameters				
Stiffness index	103 ± 18	104 ± 19	102 ± 19	0.02
Speed of sound (m/s)	1585 ± 41	1585 ± 45	1580 ± 40	0.03
Broadband attenuation (db/Mhz)	120 ± 14	120 ± 14	119 ± 16	< 0.001
Osteoporotic fracture	9.0	10.8	14.9	< 0.001
Medication				
Statin	15.4	20.6	34.2	< 0.001
Vitamin D supplementation	15.9	20.0	25.2	< 0.001
Calcium supplementation	16.0	20.4	24.7	< 0.001
Hormonal replacement	7.8	9.5	9.6	< 0.001
Benzodiazepines	5.6	6.8	11.1	< 0.001
ACE inhibitors	12.9	17.8	38.6	< 0.001
Beta-blockers	4.7	7.2	16.6	< 0.001
Diuretics				
Loop diuretics	0.2	0.3	0.8	0.01
Thiazide diuretics	0.9	2.1	4.3	< 0.001
Calcium channel blockers	4.3	6.1	14.6	< 0.001

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentage. p value is obtained with ANOVA Fisher test for continuous variables and an exact Fisher test for categorical variables

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *METs* metabolic equivalents, *ACE* angiotensin-converting enzyme

hormonal replacement therapy and benzodiazepine usage were not associated with fractures in either CKD group, eGFR levels significantly increased the magnitude of their association with fracture status. Vitamin D supplementation (positively), antihypertensives, and ACE inhibitor usage (inversely) were only associated with fracture status in CKD stage 2 individuals. CKD status, but not eGFR levels, significantly modified their association with fracture status.

Discussion

In this large population-based survey, we observed that CKD stages 2 and 3 are not associated with an increase in fracture status and do not modify the association between QUS parameters and fracture status on a multiplicative scale. We also observed that CKD status and eGFR levels modify the association between several clinical, pharmacological factors and

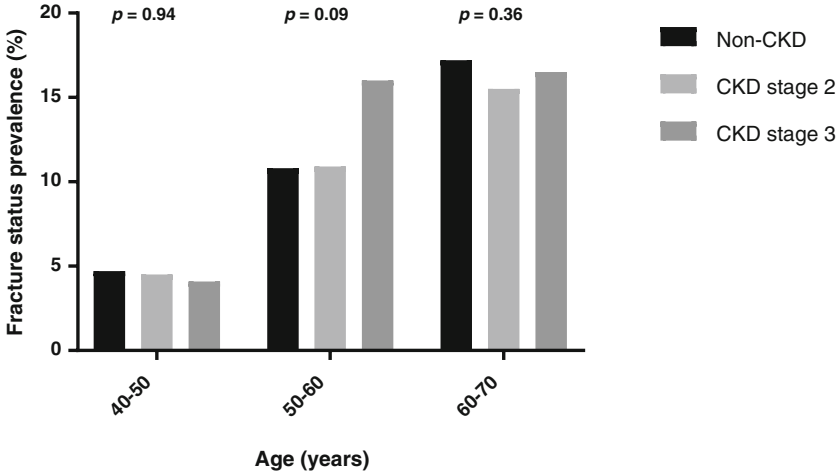

Fig. 2 Prevalence of fracture status by CKD stage after stratification for age. This figure presents the prevalence of fracture status in each of the CKD subgroups after stratification for age. *p* values are obtained with a global fisher test. CKD, chronic kidney disease

fracture status. These findings enhance our understanding of fracture risk in mild to moderate CKD and highlight the similarities and differences of bone disease between CKD and non-CKD individuals.

End-stage renal disease is recognized as a risk factor for fracture. Indeed, hip fracture incidence is four times higher in ESRD compared to the general population [5–7]. In earlier stages of CKD, there is already an elevation of bone markers such as FGF23 and Wnt inhibitors that may negatively affect bone metabolism and contribute to the increased bone fragility [1, 25, 26]. Whether early CKD is associated with an increase in fracture risk is currently unclear as previous studies have reported opposite results [3, 11–13, 15–17]. In this study, we have observed that early CKD was not associated with an increase in fracture status after stratification for age and adjustment for confounding factors. Our results are coherent with previous observational studies in moderate CKD populations showing no increased fracture incidence in CKD stage 3 populations after adjustment for demographics and comorbidities [13, 15–17]. Interestingly, our results are also coherent with a recent Canadian study that reported no increase in fracture risk in CKD stage 3 individuals < 65 years compared to non-CKD [27]. In contrast, two recent cohort studies reported that CKD stage 3 individuals had indeed an increased risk of hip fracture [3, 11]. In a case-control study of the *Women Health Initiative* cohort, eGFR measured with cystatin C was associated with an increased risk of hip fracture after adjustment for demographics and comorbidities [12]. Furthermore, an analysis of the *Longitudinal Aging Study Amsterdam* observed that CKD stage 3 was associated with increased fracture risk [28]. Several factors may explain the differences between these results and ours. These studies have often studied only hip fractures, while we have considered all anatomical sites of fractures. More importantly, these studies

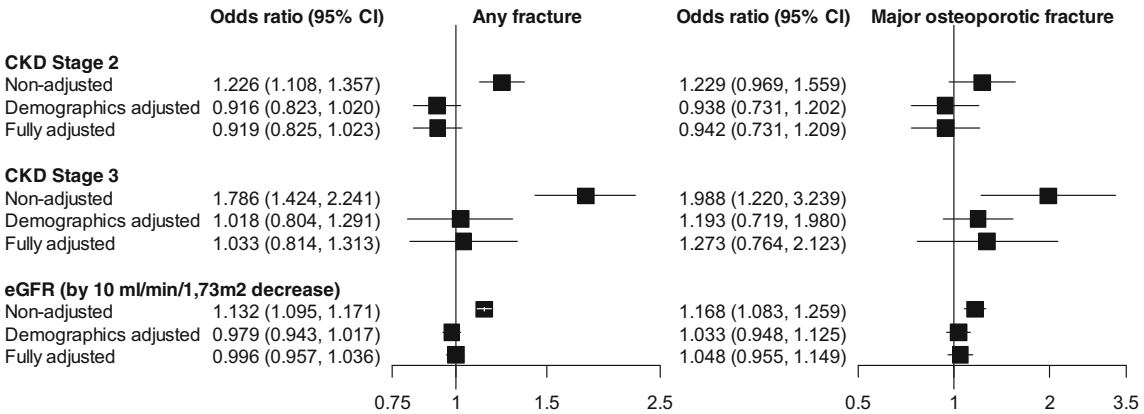

Fig. 3 Associations between CKD stage, eGFR, and fracture status. Associations between early renal disease and fracture status are presented with CKD as a categorical variable (CKD stage 2, 3 compared to non-CKD) and a continuous variable (decrease of 10 ml/min/1.73 m^2 of eGFR). Demographic model is adjusted for age, gender, and ethnicity. Fully adjusted model is adjusted for age, gender, ethnicity, smoking, cardiovascular disease, diabetes, physical activity levels, hormonal replacement therapy, calcium supplementation, vitamin D, benzodiazepines, antipsychotics, and antihypertensive medication. CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

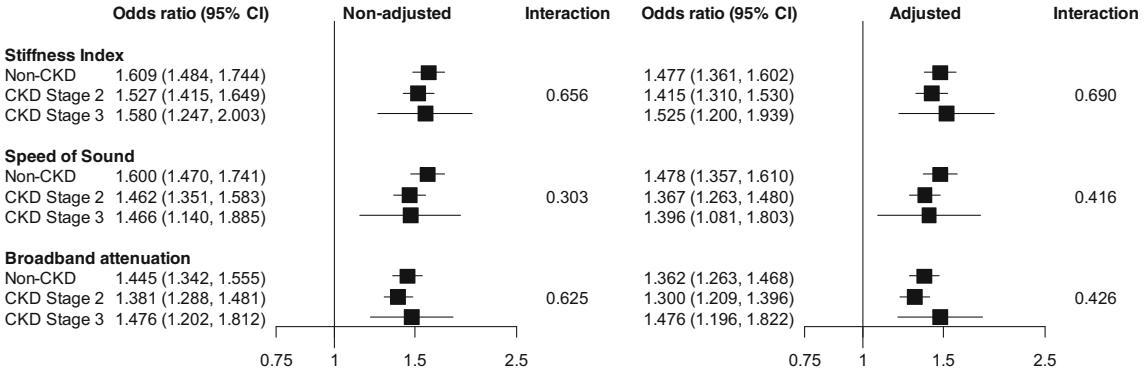

Fig. 4 Associations between QUS parameters and fracture status in CKD subgroups. The associations between QUS parameters (expressed continuously as 1 standard deviation decrease) and fracture status are stratified by CKD subgroup. Adjusted for age, gender, and ethnicity. *p* values for interaction are obtained by testing a multiplicative interaction term between CKD stage (as a categorical variable) and each QUS parameter. CI, confidence interval; CKD, chronic kidney disease; QUS, quantitative ultrasound

included older patients with significantly more advanced CKD, while we have studied middle-aged adults with early CKD where the fracture risk may be lower.

We then observed that stage 2 and 3 CKD do not modify the association between calcaneal quantitative ultrasound parameters and fracture status. This observation is coherent with previous work on the association between BMD and fractures in moderate CKD. A recent meta-analysis reported that BMD was significantly lower in fractured vs non-fractured pre-dialyzed CKD patients [10]. An observational study also observed that baseline BMD was significantly lower in pre-dialysis CKD patients with incident fractures [29] while femoral neck BMD t-score predicted incident fractures similarly in CKD and non-CKD individuals [30]. In contrast to our work, these studies were of small sample size, included patients with more advanced CKD, and mostly did not compare CKD and non-CKD patients.

Finally, our findings show that CKD modifies the association between several risk factors and fracture status. Indeed, we observed that both systolic and diastolic blood pressure were associated with increased fracture status in non-CKD patients. These results are coherent with two previous cross-sectional studies conducted in the general population that associated hypertension with increased fracture status [18, 31] and from a large Swedish cohort study that associated cardiovascular disease with the incidence of hip fracture [32]. In contrast, we showed that this association was not consistent across CKD stage 2 and 3 individuals. While the link between fractures and blood pressure has not been specifically studied in CKD populations, the association between kidney disease progression, bone, and arterial abnormalities has been previously reported [33–35]. Therefore, we can hypothesize that the interaction between CKD and blood pressure may be related to the effects of early CKD on bone and vessels axis. In addition, we have observed that CKD status or eGFR levels modified the association between hormonal replacement therapy, vitamin D supplementation, benzodiazepines, and fracture status. Since the publication of the *Women's Health Initiative* results in 2003, several studies have associated hormone replacement therapy with increased BMD and decreased osteoporotic fracture [36, 37]. In this study, we did not observe a significant association between hormone therapy in each of the CKD subgroups but observed a significant modification effect of decreased eGFR on hormone therapy usage and fracture status. This effect may reflect pathophysiological differences between osteoporosis and CKD-MBD and warrant further investigation. Similarly, the magnitude of the association between benzodiazepine usage and fracture status was increased with early CKD. The deleterious effect of this medication has been extensively studied in the general population [38], but the interaction with CKD stage has not been reported yet. Finally, vitamin D supplementation was not associated with fracture in non-CKD and stage 3 CKD individuals but was associated with increased fracture in stage 2 CKD. While the lack of association between vitamin D supplementation and fracture in non-CKD is in line with the results of two recent systematic reviews [39, 40], its positive association in stage 2 CKD individuals may be the result of an indication bias in our cohort. In this study, we also observed that the interactions between renal disease and comorbidities were different whether eGFR levels or CKD stage were used to express renal disease. This may be related to the severity of renal disease that is needed to influence the association between a risk factor and fracture status. Indeed, associations between some risk factors and fracture status may be influenced by only small decreases in eGFR, thus yielding a significant interaction term with eGFR levels but not CKD stages.

Our study has limitations. We used self-reported fracture provided in the CARTaGENE health questionnaire which could be influenced by misclassification and memory bias and may also underestimate the prevalence of vertebral fractures. While traumatic and non-traumatic fracture could not be discriminated, we nevertheless excluded fracture sites (toe,

Table 2 Factors associated with fracture status in CKD and non-CKD individuals

	Non-CKD ($n = 8725$)	CKD stage 2 ($n = 8227$)	CKD stage 3 ($n = 656$)	p value for interaction	
				CKD status	eGFR
Clinical parameters					
BMI	1.04 (0.96, 1.12)	1.02 (0.94, 1.10)	1.10 (0.91, 1.31)	0.75	0.23
Diabetes	0.94 (0.73, 1.22)	0.92 (0.72, 1.18)	1.50 (0.91, 2.45)	0.21	0.38
Cardiovascular disease	1.19 (0.88, 1.61)	1.05 (0.82, 1.34)	1.14 (0.64, 2.04)	0.81	0.45
Smoking	1.11 (0.80, 1.55)	1.36 (0.96, 1.93)	0.62 (0.14, 2.72)	0.48	0.46
Systolic blood pressure	1.08 (1.01, 1.17)*	0.90 (0.84, 0.97)*	1.10 (0.89, 1.36)	0.001	0.08
Diastolic blood pressure	1.10 (1.03, 1.19)*	1.03 (0.96, 1.11)	1.33 (1.07, 1.65)*	0.06	0.93
Heart rate	1.00 (0.93, 1.08)	1.04 (0.97, 1.12)	1.24 (1.02, 1.51)*	0.15	0.11
Biochemical parameters					
Total cholesterol	1.12 (1.04, 1.21)*	1.03 (0.96, 1.10)	1.20 (1.00, 1.46)	0.12	0.42
Uric acid	1.02 (0.94, 1.11)	1.02 (0.94, 1.10)	1.08 (0.88, 1.31)	0.87	0.67
Medication					
Statin	1.05 (0.86, 1.27)	0.84 (0.71, 1.00)	0.86 (0.54, 1.36)	0.23	0.28
Hormone replacement therapy	0.89 (0.68, 1.16)	1.12 (0.89, 1.41)	1.16 (0.58, 2.33)	0.39	0.06
Vitamin D supplementation	1.14 (0.94, 1.38)	1.24 (1.05, 1.47)*	0.67 (0.40, 1.14)	0.09	0.36
Calcium supplementation	1.12 (0.92, 1.36)	1.23 (1.03, 1.45)*	0.79 (0.47, 1.32)	0.25	0.45
Benzodiazepines	1.14 (0.86, 1.53)	1.23 (0.96, 1.58)	1.73 (0.95, 3.15)	0.48	0.08
Antipsychotics	1.61 (0.95, 2.70)	1.27 (0.77, 2.10)	1.87 (0.61, 5.74)	0.74	0.52
Antihypertensives	0.98 (0.81, 1.18)	0.82 (0.70, 0.97)*	1.46 (0.93, 2.27)	0.04	0.94
β-Blockers	1.01 (0.73, 1.39)	0.76 (0.58, 1.00)*	0.81 (0.45, 1.45)	0.41	0.39
Loop diuretics	2.82 (0.76, 10.4)	0.34 (0.04, 2.57)	NE	0.23	0.14
Thiazide diuretics	1.35 (0.70, 2.60)	1.33 (0.87, 2.01)	1.84 (0.78, 4.33)	0.79	0.34
Calcium channel blockers	1.03 (0.74, 1.43)	0.79 (0.59, 1.06)	1.36 (0.78, 2.37)	0.18	0.94
ACE inhibitors	0.91 (0.74, 1.13)	0.75 (0.62, 0.91)*	1.33 (0.86, 2.06)	0.04	0.77

Association between clinical, biochemical, pharmacological factors and fracture is expressed as odds ratio (95% confidence interval) and is adjusted for age and sex. The association between continuous parameters (BMI, blood pressure, heart rate, total cholesterol, uric acid) and fracture status is expressed for an increase of a standard deviation

ACE angiotensin-converting enzyme, *BMI* body mass index, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *NE* non-estimable

*p value < 0.05; **p value < 0.001

finger, face, and patella) that are not associated with fragility fractures to mitigate this issue. Furthermore, calcaneal quantitative ultrasound was measured instead of the standard DXA. Nevertheless, it was previously reported that calcaneal QUS correlates well with DXA at various sites and recent meta-analyses showed its association with fracture [41–44]. In addition, the small number of vertebral fractures prevented us from evaluating the association between QUS parameters and vertebral fracture prevalence. Also, our assessment of CKD status was based on a single creatinine measurement that may have misclassified some individuals. Finally, mineral metabolism parameters such as blood calcium, phosphate, and parathyroid hormone levels were not available for all participants. However, as these patients had early stage 2 and 3 CKD, we did not expect to find abnormalities in these parameters [25, 45]. Our study also has several strengths. We used a large population-based survey representative of an occidental population with a significant number of fracture events. We also assessed fracture risk in relatively young and healthy stage 2 and 3 CKD patients, which have not been well studied before. Furthermore, we included in our study all fracture sites that were compatible with fragility fracture.

In conclusion, in this analysis of a large population-based survey, we observed that stage 2 and 3 CKD were not associated with an increase in fracture prevalence, did not modify the association between calcaneal QUS and fracture status but modified the association between clinical, pharmacological parameters and fracture status. Our findings contribute to a better understanding of fracture risk in early CKD populations.

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Compliance with ethical standards

All participants signed informed consent. This study adhered to Helsinki Declaration and has been approved by appropriate ethics committees.

Conflict of interest None.

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