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Use of Renal Function Measurements for Assessing Fracture Risk in Postmenopausal Women

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Abstract

OBJECTIVE: To determine whether factors associated with moderate chronic kidney disease can be used to independently predict fracture risk in postmenopausal white women by analyzing the effect of adding renal function measurements to traditional risk factors (eg, age, body weight, bone mineral density) for fracture risk assessment.

PARTICIPANTS AND METHODS: In a prospective, population-based cohort study, postmenopausal women residing in Rochester, MN, with baseline measurements of bone mineral density and renal function were followed up for as long as 25 years for occurrence of fractures. Participants were enrolled in 1980-1984 or 1991-1993, and outcomes were analyzed in 2007. Standardized incidence ratios were used to compare the number of observed fractures with the number of predicted fractures, and potential risk factors were evaluated with Andersen-Gill time-to-fracture regression models.

RESULTS: During 5948 person-years of follow-up of 427 women, 254 women (59.5%) experienced a total of 563 fractures, 394 (70.0%) of which resulted from moderate trauma. Excluding incidentally diagnosed fractures, the 186 clinically diagnosed fractures were statistically undifferentiated from the 195 predicted fractures (standardized incidence ratio, 0.95; 95% confidence interval, 0.82-1.10). No significant trends were observed toward increasing fracture risk with inclusion of quintiles of declining renal function ($P > .10$). In univariate analyses, serum creatinine concentration, creatinine clearance rate, and estimated glomerular filtration rate were associated with greater risk of some fractures. In multivariate analyses, however, decreasing renal function was not found to be a significant risk factor, after adjusting for age, body weight, and bone mineral density.

CONCLUSION: The addition of serum creatinine concentration, creatinine clearance rate, or estimated glomerular filtration rate does not improve fracture risk prediction in postmenopausal white women who have moderate chronic kidney disease. This result can be partly explained by the fact that important risk factors for decreased renal function (eg, advanced age, lower body weight) are already accounted for in most fracture prediction models.

There is growing recognition that impaired renal function (ie, chronic kidney disease [CKD]) is common in the general population. Eight percent of adults in the United States have impaired renal function, defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m².¹ The number of people with reduced eGFR may outnumber those with end-stage renal disease by a ratio of 20 to 1.²

When a person's glomerular filtration rate (GFR) decreases to less than 40 to 50 mL/min per 1.73 m², the kidneys are unable to synthesize normal amounts of calcitriol (1,25-dihydroxyvitamin D₃), hyperphosphatemia tends to develop, and serum parathyroid hormone levels increase.³⁻⁵ End-stage renal disease (GFR <15 mL/min per 1.73 m² or requirement for long-term dialysis) is accompanied by worsening of these same determinants of abnormal bone metabolism.³⁻⁵ Thus, it is not surprising that the risk of hip fractures is increased among patients undergoing dialysis,⁶⁻⁸ as well as among patients with CKD.^{9,10}

Fracture risk has also been shown to be elevated in patients after renal transplant.¹¹⁻¹³ More relevant to the general population, however, is the observation that reduced GFR is associated with decreased bone mineral density (BMD),¹⁴⁻¹⁶ a surrogate marker for bone strength and the predominant determinant of fracture risk used in clinical decision making.¹⁷ These facts suggest that a large segment of the population (ie, those with moderately impaired renal function) could be at risk for clinically important metabolic bone disease.

It has been suggested that measurements of eGFR be introduced as a screening test to identify high-risk candidates in need of osteoporosis prophylaxis and/or skeletal health evaluation.¹⁸ However, eGFR includes clinical information (eg, age, sex, body weight) already represented among the risk factors currently used in fracture prediction models.¹⁹ Thus, it is known that both renal function^{2,16,20-24} and BMD^{25,26} decrease with age as fracture risk increases.²⁷

Moreover, it is well recognized that reduced body weight is strongly associated with fracture risk, independently of BMD.²⁸ The serum creatinine (S_{Cr}) level is related to the muscle mass of an individual.²⁹ Because muscle mass has strong associations with both body weight and age, the influence of the S_{Cr} level, eGFR, and creatinine clearance may already be reflected within the major traditional risk factors for fracture.

Consequently, it is unclear if an assessment of renal function would contribute to fracture risk prediction over and above a simple body weight measurement or a bone density assessment. Questions about this issue have recently been highlighted by an analysis that found no association between hip BMD and renal function after adjusting for age, body weight, and sex.¹⁴

The purpose of the current report is to evaluate the capability of measurements of moderately reduced renal function (ie, creatinine clearance rate and eGFR), relative to age, body weight, and BMD, to predict long-term fracture risk among postmenopausal white women, the group at greatest risk of age-related fractures.²⁷

PARTICIPANTS AND METHODS

After approval by the Mayo Clinic Institutional Review Board, participants were recruited from age-stratified random samples of residents of Rochester, MN. Two previously described cohorts were combined for this analysis. Cohort A was recruited from a random sample of Rochester women attended at Mayo Clinic in 1979-1981 who were enrolled between January 4, 1980, and March 25, 1984; women in cohort B were enrolled between September 16, 1991, and April 23, 1993, from among Rochester women sampled in 1989-1991.³⁰ The occurrence of fractures was analyzed in 2007.

Because most of the Rochester population is seen at Mayo Clinic in any 3-year period and more than half in any given year, the population enumerated in the sampling frames of the current study approximated the underlying population of the community. This population included both free-living and institutionalized individuals.³¹ We sought to enroll approximately 50 postmenopausal women per decade of age (beginning at age 30 years) in

each cohort. Women were ineligible if they had dementia or if they declined to authorize the use of their medical records for research.³²⁻³⁴

Risk Factor Assessment

After providing written informed consent, participants were interviewed at baseline in accordance with a standardized protocol to collect clinical, demographic, and lifestyle data. As described in detail in a previous report,³⁵ there was moderate to near perfect agreement ($\kappa=0.55-0.96$) between participants' interview data and their subsequent medical record reviews. When disagreements between interviews and record reviews occurred, priority was given to participants' documented medical histories.

At the time of interview, each participant also underwent anthropometric assessment, which included measurements of her height and weight.

Renal Function

Concentrations of S_{Cr} and urine creatinine were determined by using a modified Jaffe method (Multistat III Plus; Instrumentation Laboratory, Lexington, MA). Each participant provided a 24-hour urine sample. Creatinine clearance rate (mL/min; to convert to mL/s/m², multiply by 0.0167) was defined as urine creatinine concentration (mg/dL) multiplied by urine volume (mL) divided by S_{Cr} concentration (mg/dL; to convert to $\mu\text{mol/L}$, multiply by 88.4). The creatinine clearance rate was standardized to mL/min per 1.73 m² by multiplying by 1.73/body surface area. The body surface area was estimated from each participant's height and weight by using the equation developed by Dubois and Dubois.³⁶

We defined eGFR in 2 ways—using both the Modification of Diet in Renal Disease (MDRD) equation¹⁸ and the Mayo Clinic Quadratic (MCQ) equation,³⁷ as follows:

$$\begin{aligned} \text{GFR} - \text{MDRD} \left(\text{mL/min per } 1.73 \text{ m}^2 \right) &= 186 \times S_{Cr}^{-1.154} \\ &\times \text{Age}^{-0.203} \times 0.742 \text{ (if female)} \\ &\times 1.210 \text{ (if African American)} \end{aligned}$$

$$\begin{aligned} \text{GFR} - \text{MCQ} \left(\text{mL/min per } 1.73 \text{ m}^2 \right) &= \exp \left[1.911 \right. \\ &\left. + \frac{5.249}{S_{Cr}} - \frac{2.114}{S_{Cr}^2} - 0.00686 \right. \\ &\left. \times \text{Age} - 0.205 \text{ (if female)} \right] \\ &\text{(If } S_{Cr} < 0.8, 0.8 \text{ was used.)} \end{aligned}$$

In the above equations, S_{Cr} is given in mg/dL, and age is given in years.

Bone Densitometry

At baseline, areal BMDs (g/cm²) for cohort A were determined by dual-photon absorptiometry (DPA) using a prototype instrument with a precision (ie, coefficient of variation) of 2.2% for femoral neck BMD.³⁸ These data were subsequently converted to equivalent values for dual-energy x-ray absorptiometry (DEXA) by using phantom measures and crossover data from patients ($r=0.87$). Baseline DEXA measurements for cohort B were made by using a QDR 1000 densitometer (Hologic, Waltham, MA) with a coefficient of variation of 1.8% for femoral neck BMD.³³

Because there were differences between participants' DPA and DEXA results in some of the hip regions assessed, the analysis is limited to an examination of fracture prediction by femoral neck BMD, the recommended measurement site for fracture risk stratification.³⁹ The techniques of DPA and DEXA produced similar results for predicting fractures at this site.^{32,33}

Fracture Follow-up

The women enrolled were followed up for the occurrence of any new fracture by using periodic interviews and reviews of each participant's medical records from every local health care system where she received care. These community medical records encompassed all inpatient hospitalizations, outpatient and office visits, emergency department records, and local nursing home records, as well as all radiographic and pathologic reports, including autopsies. The medical records also contained the clinical history and the radiologist's report of each fracture, but the original radiographs were not available for review. Consequently, vertebral fractures were accepted on the basis of a radiologist's report of compression, wedging, or collapse of 1 or more thoracic or lumbar vertebrae.

We previously showed that clinically evident fractures (ie, those formally diagnosed in the medical record) are typically restricted to patients with more severe vertebral deformities.⁴⁰ Because we reviewed all inpatient and outpatient records for each participant, we think that ascertainment of clinically evident fractures is complete. We also included in the follow-up analyses fractures of the verte-brae and ribs that were noted incidentally on radiographs obtained for other purposes.

Statistical Analyses

Fracture risk in the combined cohort was evaluated using 2 methods of analysis, both performed with SAS statistical software (version 9.1; SAS Institute, Cary, NC).

In the first method of statistical analysis, standardized incidence ratios (SIRs) were calculated, comparing the number of first fractures observed during follow-up at each skeletal site with the number of fractures expected at those sites. Expected fracture numbers were derived by applying sex-specific and age-specific incidence rates for these fractures⁴⁰⁻⁴⁶ to the age-specific person-years of follow-up and summing over all age strata.

We calculated 95% confidence intervals (95% CI) for the SIRs by assuming that the expected fracture rates are fixed and that the observed fractures follow a Poisson distribution.⁴⁷ Generalized linear models (including log link and Poisson error) were then used to test for equality and linear trend in SIR across eGFR quintiles. The dependent variable was the occurrence of a first fracture, with the log of each participant's expected probability of a first fracture used as an offset term.

In the second method of statistical analysis, Andersen-Gill time-to-fracture regression models⁴⁸ were used to assess the effect of various participant-level covariates (eg, age, body weight, BMD, renal function) on the subsequent risk of fracture. These Andersen-Gill models allow for analysis of multiple fractures per participant while appropriately accounting for the correlation. The hazard ratios derived from this analysis represent the risk of all fractures (eg, first, second, third), in contrast to the standard hazard ratios derived from Cox proportional hazards models, which represent the risk of only first fracture.

Univariate associations between the risk of specific fractures and each clinical characteristic under consideration were assessed. We then estimated the effects on fracture risk of adding measurements of eGFR (both MDRD and MCQ), creatinine clearance rate, and S_{Cr} concentration, adjusted for the baseline values of age, body weight, and femoral neck BMD.

RESULTS

To enroll about 50 women per decade of age in cohort A, 541 women aged 30 years or older were sampled.³² Thirty-eight (7%) of these women were deemed to be ineligible for study, mainly because of dementia. Of the 503 women eligible for cohort A, 304 (60%) agreed to

participate.³² Following the same procedure, of 812 eligible women in cohort B, 351 (43%) agreed to participate.³³

Of these 655 women, only the 438 (67%) who were postmenopausal (225 in cohort A, 213 in cohort B) were considered for the current analysis. However, 11 of these women declined to authorize the use of their medical records for research.³⁴ Thus, 427 postmenopausal women were ultimately included in the analysis (220 in cohort A, 207 in cohort B), 99% of whom were white.

Because of the age-stratified sampling strategy used, women in the 2 cohorts were of comparable age (median, 68 years). In addition, the renal function of women in both cohorts was comparable, as assessed by the 3 creatinine-based methods shown in Table 1. Consequently, the 2 groups were combined for analysis.

The 427 postmenopausal women were followed up for as long as 25 years (median, 14 years); survival was found to be unimpaired. At 20-year follow-up, 47% (Kaplan Meier estimate) of participants were still alive, compared with a 42% expected survival rate ($P<.001$) based on death rates for Minnesota white women.

During 5948 person-years of observation, 254 women (59.5%) experienced a total of 563 fractures, as delineated in Table 2. Of these fractures, 13.5% were caused by severe trauma (eg, motor vehicle crashes, falls from heights), whereas 70.0% of the fractures were the result of moderate trauma (eg, normal daily activities or falls from standing height or lower). The precipitating causes or 15.1% of the fractures could not be assigned with confidence; however, they were almost certainly moderate trauma (eg, indicated by person found lying on the floor after a fall). Eight (1.4%) of the 563 fractures were pathologic in nature.

Overall, 186 clinically diagnosed fractures, excluding incidentally diagnosed rib fractures and vertebral deformities noted only on radiologists' reports, were observed among study participants. This number was statistically undifferentiated from the 195 expected fractures for these women, based on fracture incidence rates among women in the community (SIR, 0.95; 95% CI, 0.82-1.10).

The SIRs for risk of first fracture are presented in Table 3 by quintile of renal function, as assessed by the 3 creatinine-based methods. Differences in fracture risk across the quintiles of renal function were minimal, regardless of which assessment method was used. There was no evidence of a linear trend in fracture risk with renal function quintiles. Specifically, when considering the outcome of any fracture resulting from moderate trauma or osteoporosis (ie, moderate trauma fractures of the hip, spine, or distal forearm), no significant association was found between increase in fracture risk and declining renal function, as assessed by any of the methods.

Although there was a statistically significant difference between renal function quintiles in the relative risk of osteoporotic fracture as assessed by eGFR-MDRD ($P=.008$), this difference did not indicate a consistent linear trend toward increasing relative risk of fracture with low eGFR ($P=.53$). This lack of a consistent linear trend was demonstrated by the fact that the highest SIR was in the renal quintile with the highest eGFR, whereas the lowest risks for fracture were in the renal quintiles with the middle and lowest eGFRs.

The univariate and multivariate hazard ratios for development of new fractures are presented in Table 4 (any new fracture), Table 5 (any new moderate trauma fracture), and Table 6 (any new moderate trauma fracture of the proximal femur), in which renal function is treated as a continuous variable and all (ie, not just first) fractures are included. In the univariate analysis, decreased renal function, as assessed by eGFR-MCQ or creatinine clearance rate (but not by

eGFR-MDRD or S_{Cr} level), was associated with increased risk of any fracture, excluding incidental vertebral and rib fractures (Table 4). However, eGFR-MDRD, eGFR-MCQ, and creatinine clearance rate were also correlated with age (r^2 [coefficient of determination] = 0.29, $r^2=0.63$, and $r^2=0.34$, respectively; $P<.001$). Age was independently associated with fracture risk, as expected.

Lower femoral neck BMD was a risk factor for fractures, whereas greater body weight was a protective factor. Participants' membership in cohort A or cohort B did not influence fracture risk. When we adjusted for age alone (data not shown) or for age, BMD, and body weight together, none of the 3 measures of glomerular filtration/creatinine clearance rate or the S_{Cr} level were found to be associated with fractures. However, lower femoral neck BMD was a predictor of elevated fracture risk in each analysis (Table 4). Furthermore, the association between BMD and fracture risk was not dependent on renal function (ie, interactions between BMD and estimated renal function were not statistically significant).

Results almost identical to those for any new fracture (Table 4) were seen for the subset of all fractures caused by moderate trauma (Table 5), for the subset of hip (ie, proximal femur) fractures caused by moderate trauma (Table 6), and for all osteoporotic (ie, hip, spine, wrist) fractures caused by moderate trauma (data not shown).

DISCUSSION

Although BMD measurements by DEXA provide the basis for diagnosing osteoporosis,¹⁷ this approach has substantial limitations with respect to assessing future fracture risk.⁴⁹ Therefore, the World Health Organization has introduced its fracture risk assessment (FRAX) algorithm, which combines femoral neck BMD measurements with clinical risk factors, including age, sex, body mass index, parental history of fracture, personal history of fracture, rheumatoid arthritis or other risk factors for “secondary” osteoporosis, long-term corticosteroid use, cigarette smoking, and excessive alcohol use.⁵⁰ The current study examined whether impaired renal function should be added to this list.

Certainly, patients with advanced CKD or end-stage renal disease are at increased risk of fractures.^{6-13,51} Secondary hyperparathyroidism can develop in these patients, as can serious abnormalities in serum calcium, serum phosphorus, and vitamin D metabolism. Such conditions, classified as “secondary” osteoporosis in the FRAX algorithm,¹⁹ must be actively managed.

By contrast, the issue being addressed in the current study is the extent to which adding a measurement of eGFR would improve fracture risk prediction over and above the clinical assessments already being made in generally asymptomatic postmenopausal women. Our results indicate that the addition of eGFR (or of measured 24-hour creatinine clearance rate) as a potential risk factor did not enhance the ability of a standard model to predict fractures in post-menopausal women.

Renal Function, Bone Metabolism, and Fracture Risk

Traditionally, the S_{Cr} concentration has been accepted as a surrogate marker for the actual GFR. Although Cockcroft and Gault²⁹ have previously shown that such factors as age, sex, and body weight are related to muscle mass—and can be used to better estimate GFR from S_{Cr} levels—the more recent MDRD study generated renewed interest in using eGFR as a predictor of GFR.¹⁸ Compared with S_{Cr} concentration, the eGFR is a more accurate predictor of the actual GFR in nephrology referral populations.

In our experience,^{22,24,37} the eGFR-MDRD may substantially underestimate true GFR in the general population, particularly in elderly women,⁵² leading to an overestimation of the prevalence of renal impairment. This underestimation of GFR would explain our observation (Table 3) that 20% of our studied population had eGFRMDRD of less than 57 mL/min per 1.73 m², whereas analysis by eGFR-MCQ yielded a greater eGFR of 74 mL/min per 1.73 m² in the lowest quintile of renal function.

Although one may question the usefulness of eGFR as a screening tool for CKD in the general population,^{52,53} we wanted to see if renal function, when measured by 3 different methods, could serve as an important independent risk factor for fractures. Our analysis suggests that the addition of eGFR did not improve the ability of a previously described model⁵⁰ to predict fractures, in part because the determination of eGFR takes into account age, sex, race, and body weight, factors that are already included in most fracture prediction models for osteoporosis. Moreover, it was recently demonstrated that low BMD in patients with CKD was associated more with these traditional osteoporosis risk factors than with kidney function per se.¹⁴

This finding does not mean, of course, that renal function has no association with bone metabolism and fracture risk. Biochemical parameters of mineral metabolism begin to change as GFR declines to 40 to 50 mL/min.⁵ These abnormalities continue to worsen as CKD advances, to include declining calcitriol levels, increasing parathyroid hormone levels, and compensatory increases in the fractional renal excretion of phosphate. At a GFR of approximately 20 to 25 mL/min, nearly all patients will have increases in serum phosphorus and parathyroid hormone levels, as well as decreases in total serum calcium and calcitriol levels.⁵ Treatment strategies to ameliorate these abnormalities include restriction of dietary phosphorus and administration of such medications as phosphorus-binding agents, vitamin D analogues, and calcimimetics.

These strategies are designed to minimize the development of metabolic bone disease in patients with kidney failure, but it is unknown if these strategies might also be necessary to decrease fracture risk before kidney failure. Some studies^{9,10} have found that patients with less advanced CKD also have an increased risk of fracture, but this finding was not confirmed in another study.¹⁶ However, easily detected metabolic complications of CKD are relatively uncommon when eGFR is between 30 and 59 mL/min per 1.73 m².⁵⁴ Among women whose renal function is only moderately impaired, our prospective data suggest that eGFR contributes little to overall fracture risk prediction over and above traditional risk factors.

Strengths and Limitations

The current study has a number of notable strengths. In particular, it exploited the data resources of the Rochester Epidemiology Project, which provides extensive demographic and medical information on the population of Rochester.³¹ Importantly, the Rochester Epidemiology Project also includes several decades of documented outcomes with regard to actual fractures. This database allowed us to conduct a population-based study with lengthy follow-up and to completely ascertain subsequent fractures described in detailed medical records spanning each participant's entire period of residency in the community. Indeed, fracture ascertainment for the participants in this study was likely more complete than for community women generally,⁴⁶ as evidenced by the large number of vertebral and rib fractures found incidentally.

The current study also has some important limitations. The relatively small sample size, with correspondingly low numbers of certain types of fractures, reduced the statistical power of the study. We were unable to calibrate the participants' S_{Cr} levels to the assays used in the eGFR equations; however, this calibration would have had little effect on our analysis using continuous eGFR or quintiles. Moreover, only 1 participant in our study had a severe reduction in GFR (<30 mL/min per 1.73 m²). A higher number of participants with severe reduction in

GFR may have changed the observed fracture rate. The low number of participants with low GFR was not surprising because the prevalence of eGFR-MDRD in the range of 15 to 29 mL/min per 1.73m² is only 0.2% to 0.4% among the general population.¹ We were, however, able to assess fracture outcomes classified by moderate reductions in GFR (30-59 mL/min per 1.73m²).¹⁸

Our findings that the addition of S_{Cr} concentration, creatinine clearance rate, or eGFR did not improve fracture risk prediction were also influenced by the fact that eGFR measurements incorporate parameters that are either directly associated with BMD (eg, age, sex, race) or indirectly associated with BMD (eg, S_{Cr} as surrogate for muscle mass).¹⁹ When renal function was assessed by cystatin C measurements, which is unrelated to lean body mass, higher levels of cystatin C were associated with a 1.26-fold increase in hip fracture risk in women.⁵⁵ However, cystatin C is a marker of inflammation that could relate to fracture risk independently of GFR.⁵⁶

The results of the current study are not generalizable to nonwhites because the Rochester population is largely white. Age-adjusted hip fracture incidence rates from Rochester are comparable to those for US whites in general.⁵⁷

Because the current analysis did not specifically account for medical therapies that may have been administered to those individuals with CKD, therapies that could have affected renal-related abnormalities in bone metabolism, we cannot comment on the necessity of these therapies for decreasing fracture occurrence in individuals with CKD. However, fracture risk may be increased among patients identified as having CKD within a comprehensive clinical context that takes into consideration progressive increases in concentrations of S_{Cr}, proteinuria, and abnormalities in urine sediment and renal imaging.

Moreover, because the presence of calcium-phosphorus-bone disorders can increase the risk of the most common cause of mortality in patients with kidney failure (ie, cardiovascular disease),⁵⁸ it may be beneficial to institute preventive strategies early in the course of CKD.

Finally, because of the high prevalence of fractures in individuals with stage 5 kidney failure (ie, GFR <15 mL/min per 1.73 m²), it is reasonable to initiate well-tolerated strategies to prevent bone loss early in CKD, before the development of kidney failure. Our analysis, however, did not address such issues.

CONCLUSION

Despite potential limitations, our study data are the only data available on the use of measurements of renal function and eGFR to predict long-term risk of fractures. More importantly, if increases in hip fractures with reduced renal function are caused by bone loss, rather than fall-related factors, one would expect to see an increase in fractures of all types. Instead, we saw no such increase in fractures generally, in moderate trauma fractures, in osteoporotic fractures, or in hip fractures after adjusting for age, body weight, and femoral neck BMD.

Thus, our data suggest that the addition of renal function measurements as a risk factor for fracture does not improve on the typical panel of risk factors (eg, age, body weight, hip BMD) used to manage osteoporosis in postmenopausal women without moderate or severe CKD. In particular, bone density measured by DEXA seems to retain its importance as a predictor for future fracture that is not obviated by consideration of eGFR.

Additional studies are needed to determine if alternative measures of renal function or kidney disease, or more refined assessments of skeletal structure and strength, can modify the conclusions of the current study.

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Glossary

BMD, bone mineral density; CKD, chronic kidney disease; DPA, dual-photon absorptiometry; DEXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MCQ, Mayo Clinic Quadratic; MDRD, Modification of Diet in Renal Disease; S_{Cr} , serum creatinine; SIR, standardized incidence ratio.

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TABLE 1

Baseline Characteristics of Women in Studied Cohorts, With Renal Function by Quintile^a

Characteristic	Cohort A ^b (n=220)	Cohort B ^c (n=207)	Total (N=427)
Age (y)	68.1±13.7	67.9±13.3	68.0±13.5
Body weight (kg)	64.5±11.6	67.1±13.1	65.7±12.4
Femoral neck BMD (g/cm ²)	0.881±0.202	0.681±0.128	0.784±0.197
Serum creatinine (mg/dL) ^d	0.904±0.197	0.855±0.184	0.880±0.192
Serum creatinine (>1.2 mg/dL), No. (%) of patients	14 (6)	9 (4)	23 (5)
eGFR-MDRD (mL/min per 1.73 m ²)			
All participants	69.6±15.9	74.6±18.1	72.0±17.1
Quintile 1 (<56.9)	47.3±7.8	50.0±6.9	48.6±7.5
Quintile 2 (56.9-66.4)	62.2±3.0	63.1±2.7	62.6±2.9
Quintile 3 (66.5-75.2)	71.3±2.7	71.7±2.6	71.5±2.7
Quintile 4 (75.3-86.4)	81.0±3.2	80.0±3.6	80.5±3.4
Quintile 5 (≥86.5)	95.5±7.6	97.0±9.0	96.5±8.6
eGFR-MCQ (mL/min per 1.73 m ²)			
All participants	83.7±15.5	85.3±14.0	84.5±14.8
Quintile 1 (<73.7)	60.5±12.8	63.3±10.5	61.7±11.8
Quintile 2 (73.7-83.1)	78.8±2.9	79.5±2.9	79.2±2.0
Quintile 3 (83.2-89.7)	86.5±1.8	85.9±2.1	86.2±1.9
Quintile 4 (89.8-96.6)	93.6±2.0	93.1±2.2	93.4±2.1
Quintile 5 (≥96.7)	101.4±3.8	101.7±4.3	101.6±4.0
Creatinine clearance rate (mL/min per 1.73 m ²) ^d			
All participants	78.7±26.6	78.6±21.3	78.7±24.2
Quintile 1 (<59.6)	43.7±12.7	50.2±7.6	46.7±11.1
Quintile 2 (59.6-71.5)	66.0±3.5	65.6±3.4	65.8±3.4
Quintile 3 (71.6-83.5)	77.7±3.8	77.5±3.3	77.6±3.6
Quintile 4 (83.6-97.9)	91.2±4.0	90.2±4.4	90.7±4.2
Quintile 5 (≥98.0)	114.1±20.1	109.9±12.1	112.1±16.9

^a Values are mean ± SD unless otherwise indicated. BMD = bone mineral density; eGFR = estimated glomerular filtration rate; MCQ = Mayo Clinic Quadratic; MDRD = Modification of Diet in Renal Disease.

^b Cohort A consists of women recruited in 1979-1981.

^c Cohort B consists of women recruited in 1989-1991.

^d SI conversion factors: To convert serum creatinine values to μmol/L, multiply by 88.4; to convert creatinine clearance rate to mL/s/m², multiply by 0.0167.

TABLE 2

Distribution of Fractures by Skeletal Site and Cause Among the 254 Postmenopausal Women With Fracture, After Baseline Assessment of Femoral Neck Bone Mineral Density and Renal Function^{a,b}

Skeletal site	Cause of fracture			Total ^d
	Severe trauma ^c	Moderate trauma ^c	Uncertain ^c	
Skull/face	1 (14.3)	5 (71.4)	1 (14.3)	7 (1.2)
Hands/fingers	10 (38.5)	10 (38.5)	5 (19.2)	26 (4.6)
Distal forearm	6 (13.3)	38 (84.4)	1 (2.2)	45 (8.0)
Other arm	2 (7.7)	24 (92.3)	0 (0.0)	26 (4.6)
Clavicle/scapula/sternum	8 (61.5)	4 (30.8)	0 (0.0)	13 (2.3)
Ribs	10 (13.0)	47 (61.0)	19 (24.7)	77 (13.7)
Thoracic/lumbar vertebrae	10 (4.3)	170 (73.3)	48 (20.7)	232 (41.2)
Other vertebrae	1 (25.0)	3 (75.0)	0 (0.0)	4 (0.7)
Pelvis	3 (11.1)	23 (85.2)	1 (3.7)	27 (4.8)
Proximal femur	4 (7.5)	47 (88.7)	1 (1.9)	53 (9.4)
Other leg	8 (24.2)	21 (63.6)	4 (12.1)	33 (5.9)
Feet/toes	13 (65.0)	2 (10.0)	5 (25.0)	20 (3.6)
All sites	76 (13.5)	394 (70.0)	85 (15.1)	563

^aValues are number (percentage) of patients. Percentages may not equal 100% because of rounding.

^bOf the 427 women included in the analysis, 173 did not experience any fracture.

^cPercentages are of each type of fracture.

^dPercentages are of total number of fractures, including 8 pathologic fractures (1 each for hands/fingers, clavicle/sternum, ribs, and proximal femur; 4 for thoracic/lumbar vertebrae) not elsewhere included in the table.

TABLE 3

Standardized Incidence Ratios for First Fracture Among 427 Postmenopausal Women, by Quintile of Renal Function, After Baseline Assessment of Femoral Neck Bone Mineral Density^a

	First fracture type		
	Any fracture	Any moderate trauma fracture	Any osteoporotic fracture
eGFR-MDRD (mL/min per 1.73 m ²)			
Quintile 1 (<56.9)	0.91 (0.64-1.24)	0.84 (0.58-1.18)	0.64 (0.39-0.99)
Quintile 2 (56.9-66.4)	1.07 (0.77-1.43)	0.96 (0.67-1.33)	1.02 (0.67-1.49)
Quintile 3 (66.5-75.2)	0.68 (0.46-0.97)	0.59 (0.37-0.88)	0.34 (0.16-0.63)
Quintile 4 (75.3-86.4)	0.97 (0.68-1.34)	0.97 (0.66-1.39)	0.66 (0.37-1.09)
Quintile 5 (≥86.5)	1.24 (0.88-1.70)	1.31 (0.89-1.86)	1.15 (0.67-1.84)
<i>P</i> value ^b	.14	.06	.008
<i>P</i> value linear trend ^c	.36	.16	.53
eGFR-MCQ (mL/min per 1.73 m ²)			
Quintile 1 (<73.7)	1.01 (0.72-1.37)	0.93 (0.65-1.30)	0.69 (0.43-1.05)
Quintile 2 (73.7-83.1)	0.96 (0.70-1.29)	0.87 (0.61-1.20)	0.87 (0.57-1.26)
Quintile 3 (83.2-89.7)	0.91 (0.65-1.23)	0.92 (0.65-1.27)	0.73 (0.46-1.10)
Quintile 4 (89.8-96.6)	0.93 (0.64-1.31)	0.95 (0.62-1.38)	0.56 (0.28-1.00)
Quintile 5 (≥96.7)	0.96 (0.64-1.39)	0.79 (0.46-1.26)	0.61 (0.46-1.26)
<i>P</i> value ^b	.99	.97	.76
<i>P</i> value linear trend ^c	.77	.75	.47
Creatinine clearance rate (mL/min per 1.73 m ²)			
Quintile 1 (<59.6)	0.80 (0.56-1.12)	0.71 (0.47-1.03)	0.61 (0.36-0.96)
Quintile 2 (59.6-71.5)	0.98 (0.71-1.33)	0.97 (0.68-1.35)	0.87 (0.56-1.28)
Quintile 3 (71.6-83.5)	0.90 (0.63-1.24)	0.87 (0.60-1.23)	0.76 (0.46-1.17)
Quintile 4 (83.6-97.9)	0.98 (0.69-1.35)	1.01 (0.69-1.44)	0.67 (0.38-1.11)
Quintile 5 (≥98.0)	1.13 (0.79-1.56)	0.96 (0.62-1.41)	0.67 (0.34-1.20)
<i>P</i> value ^b	.74	.64	.79
<i>P</i> value linear trend ^c	.22	.29	.97

^aValues are standardized incidence ratio (95% confidence interval) unless indicated otherwise. Incidentally discovered rib and vertebral fractures are excluded from this analysis. eGFR = estimated glomerular filtration rate; MCQ = Mayo Clinic Quadratic; MDRD = Modification of Diet in Renal Disease.

^b*P* value from test in which standardized incidence ratios are equal across renal function quintiles.

^c*P* value from test for a linear trend in standardized incidence ratios across renal function quintiles.

TABLE 4

Univariate and Multivariate Hazard Ratios for Development of Any New Clinically Diagnosed Fracture (n=332) Among 427 Postmenopausal Women, After Baseline Assessment of Femoral Neck BMD^a

Risk factor	Univariate model	Multivariate model				
		1	2	3	4	5
Age (per 10-y increase)	1.52 (1.36-1.70)	1.36 (1.20-1.53)	1.43 (1.27-1.62)	1.38 (1.18-1.62)	1.41 (1.22-1.60)	1.39 (1.23-1.57)
Femoral neck BMD (per SD decrease)	1.60 (1.36-1.89)	1.25 (1.05-1.49)	1.25 (1.05-1.49)	1.26 (1.06-1.49)	1.27 (1.06-1.51)	1.26 (1.06-1.49)
Body weight (per 10-unit increase)	0.79 (0.68-0.92)	0.89 (0.77-1.02)	0.89 (0.77-1.03)	0.89 (0.77-1.03)	0.90 (0.78-1.04)	0.89 (0.77-1.03)
eGFR-MDRD (per 10-unit decrease)	1.08 (0.97-1.20)	NA	0.92 (0.84-1.01)	NA	NA	NA
eGFR-MCQ (per 10-unit decrease)	1.29 (1.19-1.40)	NA	NA	0.98 (0.85-1.13)	NA	NA
Creatinine clearance rate (per 10-unit decrease)	1.10 (1.04-1.18)	NA	NA	NA	0.97 (0.90-1.04)	NA
Serum creatinine (per 0.1 mg/dL increase)	1.05 (0.96-1.15)	NA	NA	NA	NA	0.95 (0.88-1.04)

^aValues are hazard ratio (95% confidence interval), based on proportional hazard models in which the event is a fracture and the dependent variable is survival time (d) free of fracture. Multivariate models include only those risk factors with an indicated hazard ratio. Incidentally discovered rib and vertebral fractures are excluded from this analysis. BMD = bone mineral density; eGFR = estimated glomerular filtration rate; MCQ = Mayo Clinic Quadratic; MDRD = Modification of Diet in Renal Disease; NA = not applicable.

TABLE 5
Univariate and Multivariate Hazard Ratios for Development of Any New Moderate Trauma Fracture (n=263) Among 427 Postmenopausal Women, After Baseline Assessment of Femoral Neck BMD^a

Risk factor	Univariate model	Multivariate model				
		1	2	3	4	5
Age (per 10-y increase)	1.80 (1.59-2.04)	1.56 (1.37-1.79)	1.66 (1.44-1.90)	1.62 (1.36-1.93)	1.65 (1.41-1.92)	1.61 (1.41-1.84)
Femoral neck BMD (per SD decrease)	1.90 (1.59-2.27)	1.37 (1.14-1.65)	1.37 (1.14-1.65)	1.38 (1.14-1.66)	1.39 (1.15-1.68)	1.38 (1.14-1.66)
Body weight (per 10-unit increase)	0.77 (0.65-0.91)	0.91 (0.78-1.07)	0.92 (0.78-1.08)	0.91 (0.78-1.07)	0.93 (0.79-1.10)	0.92 (0.78-1.08)
eGFR-MDRD (per 10-unit decrease)	1.13 (1.01-1.27)	NA	0.92 (0.83-1.02)	NA	NA	NA
eGFR-MCQ (per 10-unit decrease)	1.39 (1.28-1.51)	NA	NA	0.96 (0.82-1.12)	NA	NA
Creatinine clearance rate (per 10-unit decrease)	1.15 (1.07-1.23)	NA	NA	NA	0.95 (0.87-1.03)	NA
Serum creatinine (per 0.1 mg/dL increase)	1.08 (0.98-1.18)	NA	NA	NA	NA	0.94 (0.86-1.03)

^aValues are hazard ratio (95% confidence interval), based on proportional hazard models in which the event is a fracture and the dependent variable is survival time (d) free of fracture. Multivariate models include only those risk factors with an indicated hazard ratio. Incidentally discovered rib and vertebral fractures are excluded from this analysis. BMD = bone mineral density; eGFR = estimated glomerular filtration rate; MCQ = Mayo Clinic Quadratic; MDRD = Modification of Diet in Renal Disease; NA = not applicable.

TABLE 6

Univariate and Multivariate Hazard Ratios for Development of Any New Moderate Trauma Proximal Femur Fracture (n=48) Among 427 Postmenopausal Women, After Baseline Assessment of Femoral Neck BMD^a

Risk factor	Univariate model	Multivariate model				
		1	2	3	4	5
Age (per 10-y increase)	2.69 (2.03-3.55)	2.29 (1.62-3.25)	2.20 (1.52-3.18)	2.31 (1.56-3.42)	2.29 (1.52-3.43)	2.28 (1.60-3.24)
Femoral neck BMD (per SD decrease)	2.53 (1.72-3.72)	1.41 (0.92-2.16)	1.40 (0.91-2.15)	1.41 (0.91-2.17)	1.40 (0.91-2.14)	1.40 (0.91-2.16)
Body weight (per 10-unit increase)	0.65 (0.48-0.90)	0.83 (0.62-1.10)	0.82 (0.62-1.09)	0.83 (0.62-1.10)	0.82 (0.61-1.11)	0.82 (0.62-1.10)
eGFR-MDRD (per 10-unit decrease)	1.45 (1.18-1.78)	NA	1.07 (0.87-1.32)	NA	NA	NA
eGFR-MCQ (per 10-unit decrease)	1.63 (1.42-1.87)	NA	NA	0.99 (0.77-1.26)	NA	NA
Creatinine clearance rate (per 10-unit decrease)	1.28 (1.12-1.45)	NA	NA	NA	1.00 (0.84-1.20)	NA
Serum creatinine (per 0.1 mg/dL increase)	1.23 (1.08-1.40)	NA	NA	NA	NA	1.01 (0.88-1.16)

^aValues are hazard ratio (95% confidence interval), based on proportional hazard models in which the event is a fracture and the dependent variable is survival time (d) free of fracture. Multivariate models include only those risk factors with an indicated hazard ratio. BMD = bone mineral density; eGFR = estimated glomerular filtration rate; MCQ = Mayo Clinic Quadratic; MDRD = Modification of Diet in Renal Disease; NA = not applicable.