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Change in estimated glomerular filtration rate and fracture risk in the Action to Control Cardiovascular Risk in Diabetes Trial

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ABSTRACT

Objective: Patients with type 2 diabetes (T2DM) are at increased risk of fracture. High prevalence of chronic kidney disease (CKD) in T2DM may contribute to bone fragility, but whether dynamic change in kidney function is associated with fracture risk is unclear.
Research design and methods: To evaluate the association of pre-randomization baseline estimated glomerular filtration (eGFR) and its change over time with subsequent fracture risk in the Bone substudy of Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial, we conducted an observational study of 2262 women and 4737 men with T2DM and with at least 2 eGFR values.
Results: During a mean follow-up of 4.40 ± 1.54 years, 235 women and 223 men sustained a new non-vertebral fracture. In multivariable adjusted sex-specific models, pre-randomization baseline eGFR was not a significant predictor of fracture risk in either men or women. However, a steeper decline in eGFR was associated with greater risk of fracture in women (hazard ratio [HR] per standard deviation [SD] decrement in eGFR slope, 1.30; 95%CI 1.17–1.44) but not men (HR per SD decrement in eGFR slope, 0.97; 95%CI 0.82–1.13). Accounting for competing risk of death modestly attenuated the association in women (HR per SD decrement in eGFR slope, 1.19; 95%CI 1.04–1.37), with the relationship in men remaining non-significant (HR per SD decrement in eGFR slope, 0.96; 95%CI 0.77–1.18).
Conclusions: Declining kidney function predicts fracture risk in women but not in men with T2DM. Future studies should investigate the mechanisms for these associations.

Introduction

Type 2 diabetes (T2DM) is a leading cause of blindness, amputations, kidney failure, and cardiovascular disease [1]. These microvascular and macrovascular complications impair functional status, shorten lifespan and increase healthcare expenditures [2]. Although T2DM is associated with significantly higher bone mass compared to the general population, it increases fracture risk, further contributing to morbidity, mortality and costs [3–6]. Incomplete understanding of the pathogenesis of bone fragility in T2DM and limited utility of bone densitometry in this population that experiences excess fracture rates in the setting of normal or high bone mass has hampered fracture risk stratification [7,8]. An enhanced understanding of clinical factors that promote decreased bone strength in T2DM could facilitate identification of individuals who are most at risk for fractures and who could be targeted for proven osteoporosis preventative measures.

The high prevalence of chronic kidney disease (CKD) in individuals with T2DM may contribute to increased bone fragility in T2DM. CKD, even early in its course, is frequently complicated by disordered bone and mineral metabolism that may promote reduced bone strength [9]. Epidemiologic studies suggest that compared to the general population, the presence of CKD, defined as reduced estimated glomerular filtration rate (eGFR) at a single point in time, confers nearly a 2-fold greater risk of hip fracture [10,11]. However, it remains uncertain if similar relationships hold true among individuals with T2DM, for whom cross-sectional eGFR assessments may carry greater imprecision compared to the general population [12]. Given that a dynamic decline over time in eGFR is a clinically-accepted and evidence-based surrogate for loss of kidney function in both diabetic and non-diabetic populations [13,14], we

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studied the relationship between longitudinal change in eGFR and the incidence of non-vertebral fractures in men and women with T2DM who participated in the Bone sub-study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial. We hypothesized that a decrease in eGFR over time is an independent risk factor for non-spine fractures in patients with T2DM and that sequential change in eGFR would outperform pre-randomization baseline eGFR as a predictor of fracture risk.

Materials and methods

Study population

The ACCORD Trial was a randomized, multi-center, double 2 × 2 factorial design study that compared the effects of intensive vs. standard glycemic control, fibrates versus placebo, and intensive versus standard blood pressure (BP) control on major cardiovascular disease events in 10,251 patients with T2DM. The study design, entry criteria, and results have been published [15,16]. Randomization occurred from 2001 to 2005. Participants in the intensive glycemic control arm achieved a median HbA1C of 6.4%, whereas the median HbA1C in the standard glycemic control arm was 7.5% [16]. After a mean treatment period of 3.7 years, the intensive glycemia intervention was stopped in 2008 due to increased all-cause mortality [16].

The ACCORD–BONE study evaluated the effect of intensive versus standard glycemic control on fracture risk. Five of the seven clinical center networks, including 54 of 77 clinical sites and 7287 of the 10,251 ACCORD participants, participated in the BONE sub-study. Participants were asked annually about the occurrence of any non-spine fractures. All fractures were confirmed by blinded central adjudication, based on radiology records [17]. The protocol was approved by the institutional review board at each study site, and all participants provided written informed consent.

We analyzed data from 6609 of the ACCORD–BONE study participants who had a month 4 serum creatinine value and at least one subsequent serum creatinine measured prior to occurrence of fracture or end of follow-up.

Exposure

The primary exposures were pre-randomization baseline eGFR and post-randomization change in eGFR expressed as eGFR "slope" (change over time). GFR was estimated from serum creatinine, measured by the Roche Creatinine Plus enzymatic method (Roche Diagnostics, Basel, Switzerland), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [18]. The month 4 serum creatinine was used as the first point in calculating eGFR change because introduction of some ACCORD interventions (including fenofibrate for those Lipid Trial participants randomized to active treatment) affected serum creatinine levels early [19]. The eGFR slope was calculated as eGFR at last visit before fracture (last visit for censored observations) minus eGFR at month 4 visit divided by time from month 4 visit to fracture or censoring. The mean time from month 4 to the last (pre-event or follow-up) serum creatinine measurement was 4.37 ± 1.57 years (median 4.35 years).

Outcome

The primary outcome was a non-vertebral fracture, which included upper extremity (hand, distal forearm, proximal humerus), lower extremity (foot, ankle, leg, hip), or axial (rib, chest/sternum, face) fracture. Reported fracture events were centrally adjudicated, based on radiology records [17]. Confirmed pathologic fractures (periprosthetic fractures or fractures occurring secondary to neoplasm, necrosis or sepsis) were excluded, but all other fractures, including those following trauma, were included. We calculated follow-up time for events and censored observations from the date of the month 4 visit rather than randomization. The mean time to fracture (or last follow-up for censored observations) was 4.40 ± 1.54 years (median 4.37 years).

Assessment of pre-randomization baseline covariates

Demographic characteristics, diabetes duration, smoking status, medical and medication history were determined at the pre-randomization baseline visit using standardized questionnaires. Height, weight and systolic BP were measured according to a standardized protocol. All pre-randomization baseline laboratory values were obtained centrally at the University of Washington Northwest Lipid Metabolism and Diabetes Research Laboratory. Urine creatinine was determined enzymatically on a Roche Double Modular P Analytics automated analyzer. Urine albumin was determined by immunonephelometry on a Siemens BN II nephelometer. HbA1c was measured by an automated high-performance liquid chromatography (Tosoh Bioscience, South San Francisco, CA). Microalbuminuria was defined as a urinary albumin to creatinine ratio of ≥30 mg/g, and macroalbuminuria was defined as urinary albumin to creatinine ratio of ≥300 mg/g.

Statistical analysis

Descriptive statistics of pre-randomization baseline characteristics were calculated overall and stratified by sex due to greater fracture risk in T2DM in women compared to men [4]. We used Cox proportional-hazards regression models to examine in sex-specific analyses the associations of pre-randomization baseline eGFR and eGFR slope with time to first non-vertebral fracture. We evaluated pre-randomization baseline eGFR as a continuous variable, with increases in risk calculated per one sex-specific standard deviation decrement in eGFR. We adjusted for the following pre-randomization baseline covariates: age, white race, living status (with others or alone), education less than high school graduate, uninsured or Medicaid patient, smoking status (ever), body mass index, systolic BP, HbA1c, diabetes duration, history of clinical cardiovascular disease (myocardial infarction, stroke, coronary, carotid or peripheral arterial revascularization procedure, positive stress test), microalbuminuria, macroalbuminuria, glycemia trial treatment assignment, second trial (BP or Lipid) treatment assignment, and use of inhaled steroids, thiazolidinediones, insulin, thiazide diuretics, loop diuretics, statins, and anti-psychotic medications. We examined models incorporating interaction terms to evaluate variation by gender in the effect of change in eGFR on the risk of fracture. Since death precludes the occurrence of fracture, we used the method of Fine and Gray to account for the competing risk of death [20]. Magnitudes of associations were assessed by hazard ratios and associated 95% confidence limits. Appropriateness of the proportional hazards assumption was assessed via examination of Martingale-based residuals [21]. All tests of significance were performed at the two-sided 5% alpha-level and analyses performed using SAS version 9.3 software (SAS Institute, Cary, NC). Proportional hazards analyses with competing risks were performed utilizing the "%PSHREG" SAS macro of Kohl and Heinze [22].

Results

The pre-randomization baseline characteristics of the 6609 ACCORD–BONE participants (Table 1) are qualitatively similar to those of the overall ACCORD, which was composed of middle-aged and older patients with poorly controlled T2DM and multiple complications [16]. The mean age was 62.5 ± 6.7 years. The mean pre-randomization baseline eGFR was 78.5 ± 18.2 ml/min/1.73 m^2, and 17% of participants had pre-randomization baseline eGFR <60 ml/min/1.73 m^2. Nearly 30% of participants had microalbuminuria, and the prevalence of macroalbuminuria was 6%. The median annualized decline in eGFR during follow-up was −1.2 ml/min/1.73 m^2/year (IQR, −3.5, 0.1).