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Reduced Fracture Risk With Early Corticosteroid Withdrawal After Kidney Transplant

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Abstract

Corticosteroid use after kidney transplantation results in severe bone loss and high fracture risk. Although corticosteroid withdrawal in the early posttransplant period has been associated with bone mass preservation, there are no published data regarding corticosteroid withdrawal and risk of fracture. We hypothesized lower fracture incidence in patients discharged from the hospital without than with corticosteroids after transplantation. From the United States Renal Data System (USRDS), 77 430 patients were identified who received their first kidney transplant from 2000 to 2006. Fracture incidence leading to hospitalization was determined from 2000 to 2007; discharge immunosuppression was determined from United Networks for Organ Sharing forms. Time-to-event analyses were used to evaluate fracture risk. Median (interquartile range) follow-up was 1448 (808–2061) days. There were 2395 fractures during follow-up; fracture incidence rates were 0.008 and 0.0058 per patient-year for recipients discharged with and without corticosteroid, respectively. Corticosteroid withdrawal was associated with a 31% fracture risk reduction (HR 0.69; 95% CI 0.59–0.81). Fractures associated with hospitalization are significantly lower with regimens that withdraw corticosteroid. As this study likely underestimates overall fracture incidence, prospective studies are needed to determine differences in overall fracture risk in patients managed with and without corticosteroids after kidney transplantation.

Keywords

Corticosteroid; fracture; immunosuppression; kidney; renal; transplantation; USRDS

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Disclosure

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Introduction

Risk of fracture after kidney transplantation is high. In comparison to the general population, there is an overall 4.5-fold greater risk of fracture (1,2). In comparison to patients on hemodialysis, risk of hip fracture is 34% greater (3). Efforts to reduce fracture risk after kidney transplantation have been disappointing; although agents typically used to treat corticosteroid-induced osteoporosis have been demonstrated to increase bone mass after transplantation, no single study of these treatments have been demonstrated to reduce fracture risk (4,5). These data are alarming as mortality rates increase more than 60% after hip fracture (1). Interventions that lower fracture incidence are urgently needed in the kidney transplant population.

Kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD). Immunosuppression regimens combining calcineurin inhibitors with corticosteroids have resulted in 1-year recipient survival exceeding 95% (6) while mortality for patients with ESRD on hemodialysis is 225 per 1000 patient-years (7). However, administration of corticosteroids results in multiple untoward clinical consequences. The high corticosteroid doses characteristic of the early posttransplant period are associated with rapid bone loss and high fracture rates (8–10). In the long term, corticosteroid doses are lowered and bone mass may partially recover (11,12); however, fracture risk remains elevated (2,13).

To alleviate complications associated with chronic corticosteroid administration, newer immunosuppression regimens with early corticosteroid withdrawal (ECSW) have been developed (14–16). Currently, more than 30% of kidney transplant recipients in the United States (US) are managed with antibody induction therapy coupled with rapidly tapered high-dose methylprednisolone and are discharged from the hospital without corticosteroids (15). Within the first year after transplantation, resumption of corticosteroids occurs in a minority of patients (17,18) and 5-year graft survival and function rates for patients remaining on ECSW are equivalent to those discharged with corticosteroids (14,16). Several small studies have demonstrated that in comparison to corticosteroid-based immunosuppression (CSBI), corticosteroid withdrawal was associated with preserved bone mass after transplantation (19–22). However, these studies lacked statistical power to determine whether ECSW was associated with lower fracture risk than CSBI. In light of data suggesting that ECSW preserves bone early after transplant, we hypothesized that fracture rates in kidney transplant recipients discharged without corticosteroids are lower than in those who are discharged with corticosteroids. We evaluated our hypothesis using the United States Renal Data Systems (USRDS) in patients undergoing first kidney transplantation between 2000 and 2006.

Methods

Patients

The USRDS is the largest kidney transplantation registry and combines the United Networks for Organ Sharing (UNOS) transplantation registry data with payment data from the Centers for Medicare and Medicaid Services (CMMS) (23,24). We estimated incident fractures

leading to hospitalization among patients with a first kidney transplant between January 1, 2000 and December 31, 2006 (n = 77 430; CSBI = 66 266; ECSW = 11 164) who were discharged from the hospital either with or without corticosteroids. Patients were excluded for transplantation before 2000, a history of multiple kidney or other organ transplantations or graft failure within 180 days of transplantation. Follow-up continued until death, graft failure, fracture or December 31, 2007. Our reported rates of graft survival included death as cause of graft failure.

Determination of corticosteroid use at hospital discharge and date of first fracture

Fractures leading to hospitalizations were chosen because they are less subject to interpretation than outpatient cases of fractures, especially because the USRDS database has no information on radiographic studies; also these fracture rates can be compared directly to the National Center for Health Statistics (1). Corticosteroid administration at time of discharge was determined from *UNOS Immunosuppression Treatment Forms* (25) contained within USRDS, which are submitted at the time of transplantation. UNOS forms contain information regarding induction regimen and duration, type of immunosuppression maintenance at hospital discharge and the treatment of rejection episodes; however, medication doses are not included. First-time fractures resulting in hospitalization were determined from International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for fracture (ICD-9-CM codes 805.0–829.9) contained within USRDS and obtained from claims data submitted to CMMS. Both phalangeal (ICD-9-CM 816.0–816.9; 826.0–826.9) and skull (ICD9-CM 850–854) fractures were excluded. In the event of multiple fractures in the same patient, we considered first listing of a fracture specific ICD-9-CM code as the fracture event. Both traumatic and fragility fractures were included because the level of trauma associated with fracture was not completely recorded in USRDS; similar to low-trauma fractures, high-trauma fractures are associated with low bone mineral density (BMD) and increased risk of future fracture (26).

Ascertainment of fracture covariates

Fracture covariates obtained from USRDS were selected on the basis of epidemiologic studies that demonstrated their ability to predict fracture in chronic kidney disease (CKD) and kidney transplant populations (3,27–32). These included age at transplantation (years), gender, race (White, Black, Asian and Other), body mass index (BMI), HLA-matching (0; 1–2; 3–4 and 5–6), donor type (deceased or living), induction at transplant, parathyroidectomy (before or after transplantation) and a history of pretransplantation dialysis, pretransplantation fracture and pre-transplantation diabetes. BMI was evaluated both as continuous and categorical parameters: underweight (BMI <18.5), normal (BMI 18.5–24.9), overweight (BMI 25–29.9) and obese (BMI of >30). BMI >50 (n = 155) was considered a measurement error and was classified along with those missing BMI measurements (n = 12 370) as a separate covariate in analyses. Pretransplantation fracture was determined by the presence of an ICD-9-CM fracture code with a date of service before transplantation. We did not separately adjust for pretransplant peritoneal- or hemodialysis; both in univariate and multivariate models, peritoneal- and hemodialysis were associated with increased fracture risk, which was not materially different from that of a combined dialysis variable alone. We also adjusted the multivariate model for other factors associated

with kidney transplantation that may affect posttransplantation fracture risk due to necessary corticosteroid administration, including: (1) a history of rejection (yes, no), as these episodes are usually treated with corticosteroid and may result in long-term corticosteroid administration; and (2) etiologies of ESRD, such as nephrosis and nephritis, that may be treated with corticosteroids both before and after transplantation due to their underlying causes (i.e., USA systemic lupus erythematosus). Finally, our main multivariate model did not adjust for dialysis duration because a date of first dialysis was not listed for 3465 patients with a history of pretransplantation dialysis. However, we reported relationships between duration of pretransplantation dialysis and fracture based on a separate analysis that excluded patients without a dialysis start date.

Statistical analysis

Analyses were performed using STATA (version 8.2; StataCorp LP, College Station, TX, USA) and SAS (v9.2, Cary, NC, USA). Analyses were designed to: (1) compare characteristics of patients with a first transplant discharged with or without corticosteroids; (2) evaluate time to first fracture; (3) quantify fracture risk by immunosuppression regimen at discharge while controlling for fracture covariates and (4) evaluate modulation of fracture risk according to corticosteroid use at discharge, considering both modifiable and nonmodifiable fracture risk factors. Categorical and continuous parameters were compared using chi-square and Student *t*-tests, respectively. Time to first fracture and patient and graft survival were modeled using the Kaplan–Meier method, with the log-rank test. Proportional hazard regression was used to quantify fracture risk with ECSW in comparison to CSBI, while adjusting for covariates of fracture determined from univariate analyses. Preliminary diagnostics revealed nonproportional hazards for fracture (i.e. fracture risk varied with time). To model this association the main hazard model was stratified by follow-up time at 3 years. To evaluate modulation of fracture risk by corticosteroid use at discharge, the hazard model was scored by logistic regression. Fracture risk for a transplant recipient with both modifiable (pretransplant dialysis) and nonmodifiable (age, gender, race and pretransplant diabetes) risk factors for fracture was then stratified by corticosteroid at discharge and presented as the population median (interquartile range [IQR]) risk. Finally, in a randomized clinical trial risk factors for fracture would have been evenly distributed between ECSW and CSBI groups. However, in this observational study, multiple fracture covariates were unequally distributed between immunosuppression groups. Therefore, in order to validate our findings, we conducted a separate analysis (data not presented) using propensity scores for corticosteroid administration at discharge (33). Inclusion of propensity score as a covariate in the model of interest (outcome = fracture) did not substantially alter results.

Results

Cohort characteristics

Using the USRDS, 77 430 adults who had a first kidney transplant between January 1, 2000 and December 31, 2006 were identified. Immunosuppression regimen at hospital discharge was determined. Follow-up data regarding both immunosuppression and acute rejection were incomplete; UNOS reported rates of rejection were significantly lower in patients discharged without than with corticosteroid (8.6% vs. 13.1%, *p*-value < 0.001). Graft

survival in patients managed with ECSW was equivalent to those managed with CSBI at 1 year (96.1% vs. 95.7%; p-value = 0.07), slightly greater than in those managed with CSBI at 3 years (88.8% vs. 87.5%; p-value = 0.009) and equivalent at 5 years (80.4% vs. 78.7%; p-value = 0.1). For ECSW, patient survival was equivalent at 1 year (96.9% vs. 96.7% with CSBI; p = 0.3) but was slightly greater at 3 years (92.6% vs. 91.6% with CSBI; p-value = 0.01) and 5 years (87.2% vs. 85.1% with CSBI; p-value = 0.03). There were small but significant differences between patients discharged with and without corticosteroids (Table 1). Patients discharged without corticosteroids were slightly older and had a slightly higher BMI; they were more likely to be male or white, to have diabetic nephropathy, to have received induction, to have a zero HLA mismatch or received a living donor transplant and to have had a slightly shorter time on dialysis; they were less likely to have been on pre-transplant dialysis, or have undergone parathyroidectomy. Prevalence of pretransplantation fracture did not differ between groups. Consistent with previous reported rates of ECSW protocols, rates of discharge without corticosteroid increased between the years 2000 and 2006; more than 30% of recipients were discharged without corticosteroids in 2006 (14,15).

Incidence and type of fractures leading to hospitalization according to corticosteroid use at hospital discharge

Median (IQR) follow-up was 924 (600–1370) and 1501 (880–2142) days for patients discharged with and without corticosteroid, respectively. The incidence of fractures leading to hospitalizations during follow-up from January 1, 2000 to December 31, 2007 was significantly lower for patients discharged without than with corticosteroids (1.7% vs. 3.3%, respectively, p-value < 0.001); the absolute risk reduction was 1.6%. After transplantation, 2395 fractures resulting in hospitalizations were identified during 306 923 patient-years of follow-up; 5.8 and 8.0 fractures per 1000 patient-years were observed for recipients discharged without and with corticosteroid, respectively. The most common fracture sites were femur (29%), ankle (15%) and spine (11%). The distribution of fracture sites did not differ between immunosuppression groups.

Risk of fractures leading to hospitalization according to corticosteroid use at hospital discharge

Although Kaplan–Meier analysis of time to fracture demonstrated a small decrease in the incidence of fractures 12 months after transplantation in patients discharged without corticosteroids, the incidence was significantly lower at 24 months after transplantation, (p-value < 0.0001, Figure 1).

In multivariate proportional hazard regression analysis, adjusting for other fracture risk factors, there was an associated 31% (p-value < 0.001) reduction in fracture risk for patients managed with ECSW compared to CSBI (Table 2). In addition, age, female gender, low BMI, the presence of diabetes and a history of dialysis and fracture before transplantation were all significantly associated with increased risk of posttransplant fracture. Higher BMI and both Asian and Black race were protective against sustaining a fracture. Although rates of induction, rejection and parathyroidectomy differed between groups, these covariates did not affect fracture risk in multivariate analysis. In a subset analysis excluding patients without a date of first dialysis, each year of dialysis before transplantation was associated

with a 4% increased fracture risk after transplantation (HR 1.04; 95% CI 1.03–1.06); duration of pretransplantation dialysis did not affect the reduction in fracture risk associated with ECSW.

To account for variable fracture rates with time, hazard models were stratified at 3 years follow-up. Fracture risk was 26% (HR 95%CI 1.06–1.50) and 70% (HR 95%CI 1.18–2.46) higher in patients managed with CSBI, in comparison to ECSW, with less than and more than 3 years of follow-up, respectively.

Risk assessment of fractures leading to hospitalization based on postkidney transplant corticosteroid use

Modifiable risk factors for fracture, including discharge with corticosteroids and pretransplantation dialysis resulted in a 45% and 56% increased risk of fracture, respectively (Figure 2). However, nonmodifiable risk factors for fracture, including older age and a history either of pretransplantation fracture or diabetes had greater influence on fracture risk after transplantation than corticosteroid use. In order to estimate the influence of corticosteroids on fracture risk in the presence of other important risk factors for fracture, we created a risk model based on patients within USRDS who had modifiable and nonmodifiable risk factors for fracture including: pretransplantation dialysis, both older and younger age, male or female gender and the presence or absence of pretransplantation diabetes (Figure 3). In general, fracture risk was highest for recipients who were either older, female or had a history of pretransplant diabetes. ECSW resulted in decreased fracture risk for all combinations of modifiable and non-modifiable risk and resulted in a downward shift in risk for all age groups. It is noteworthy that given identical nonmodifiable risk factors for fracture, recipients age 18–50 years discharged on corticosteroids had equivalent fracture risk as recipients over 65 years discharged without corticosteroid.

Discussion

To our knowledge, these are the first published data comparing the incidence of fractures leading to hospitalization in kidney transplant patients discharged with and without corticosteroids. The results of these analyses confirm our hypothesis that kidney transplant recipients discharged without corticosteroids have a lower risk of fractures than recipients discharged with corticosteroids. The 31% risk reduction in fracture associated with ECSW became significant by 24 months after transplantation. In absolute terms, there was a 1.6% reduction in fracture risk, meaning that over 5 years, one fracture would be prevented for every 61 patients managed without corticosteroid. These data also highlight the important contributions of both traditional and CKD-specific risk factors for fracture to postkidney transplantation fracture risk; older age, previous fracture and both pretransplant diabetes and dialysis were strongly associated with fracture. We also investigated whether ECSW modulated risk in the presence of other risk factors for fracture; ECSW decreased fracture risk given any set of nonmodifiable risk factors. Considering that no single clinically effective treatment to decrease fracture risk after kidney transplant has yet been identified, ECSW may provide a single, innovative approach to minimize risk in this population that is very susceptible to fracture.

Corticosteroids are the most common cause of drug-induced osteoporosis and up to 50% of patients on corticosteroids will suffer an osteoporotic fracture (34). Even doses of prednisolone as low as 2.5 mg can increase fracture risk (35). Corticosteroids profoundly suppress osteoblast function and increase osteoblast apoptosis, resulting in reduced mineral apposition rate, prolonged mineralization lag time and an approximate 30% reduction in the amount of bone replaced in each remodeling cycle (36–40). In addition, osteoclast activity may be increased resulting in slightly enhanced bone resorption, particularly early in the course of therapy (41,42). Although coadministration of calcineurin inhibitors with corticosteroids has permitted use of lower corticosteroid doses, fracture rates remain high (1,2,9,43–45). Both Cyclosporine A and FK506 cause severe bone loss in animal models, with marked increases in resorption and formation. The combined administration of calcineurin inhibitors and corticosteroids is associated with profound uncoupling of bone remodeling. In the first 6 months after transplantation, when corticosteroid doses are highest, there is rapid bone loss between 2.4% (8,9) and 10% (10) at the lumbar spine. As corticosteroid doses are lowered, and adverse effects on formation decrease, rates of bone loss and fracture risk decline. The initial excess risk of hip fracture after transplantation compared to patients on hemodialysis subsequently decreases by 1% monthly; by approximately 630 days posttransplantation, hip fracture risk is equivalent for kidney transplant recipients and patients on hemodialysis (3). However, chronic administration of even low-dose corticosteroids results in elevated overall fracture rates (2), which are approximately 2% higher than in patients on hemodialysis (46,47). Indeed, the estimated fracture incidence 10–15 years after transplantation, reported as 17–18% (47,48) and 23% (48), respectively, is consistent with our data suggesting long-term corticosteroid exposure enhances fracture risk. In comparison to discharge without corticosteroids, less than 3 years of corticosteroid exposure was associated with a 26% increased fracture risk while more than 3 years of corticosteroid exposure was associated with a 70% increased fracture risk.

Efforts to prevent fracture after kidney transplantation have focused mainly on reducing bone loss in the early posttransplantation period. Multiple studies have demonstrated that treatment within the first year after transplantation with either a bisphosphonate (4,49–51) or 1,25(OH)₂D (4,52–54) protects against bone loss. No single study has demonstrated that preservation of bone density with any agent reduced fracture incidence. However, a meta-analysis by Palmer et al. (4) demonstrated that treatment of any type was associated with a 49% fracture risk reduction after transplantation. Although intervention trials powered to detect a reduction in fracture incidence after treatment with either a bisphosphonate or 1,25(OH)₂D are needed, the use of bisphosphonates in this population is controversial. Major concerns include the induction of acute kidney injury by intravenous bisphosphonates, prolonged duration of bisphosphonate effect because of reduced renal clearance (55), the perpetuation or induction of adynamic bone disease (49,56), the exacerbation of secondary hyperparathyroidism (57) and the possible increased risk of atypical femur fractures (58). Novel methods that decrease fracture risk but do not result in additional complications to kidney graft function or bone health are needed.

It is therefore noteworthy that the hazard ratio (0.69) we report for reduced fracture risk associated with ECSW was in the range of fracture risk reduction reported in the meta-analysis by Palmer et al. of any pharmacologic treatment for prevention of postkidney

transplant fracture (relative risk 0.51; 95% CI 0.27–0.99) (4). In addition, the number needed to treat with ECSW to prevent one fracture is 61, which is within the range reported for prevention of post-menopausal fragility fractures by bisphosphonates (59,60). Antibody induction combined with tapering, high dose, intravenous methylprednisolone followed by ECSW and chronic immunosuppression with a calcineurin inhibitor and mycophenolate mofetil, has rapidly gained acceptance as a safe and acceptable form of immunosuppression after transplantation in the United States (14). From 2000 to 2006, use of these protocols at US transplantation centers increased more than 10-fold (15). Small clinical trials have demonstrated favorable effects of corticosteroid withdrawal on bone mass in comparison to CSBI; lumbar spine and femoral neck bone density increased from 1.8 to 4.6% and from 1.6 to 2% (19–22), respectively. Conversely, bone mass decreased from 1.4 to 8.0% and from 1.6 to 2.3% at the lumbar spine and femoral neck, respectively (19–22), with coadministration of corticosteroids with calcineurin inhibitors.

Although we found the incidence of fractures requiring hospitalization in patients discharged with and without corticosteroids to be 8.0 and 5.8 per 1000 patient-years, respectively, the overall incidence of fractures is likely much higher. A previous study found that USRDS estimates of fractures leading to hospitalizations vastly underestimated overall fracture rates (1,2). Indeed, using the USRDS to assess overall fracture rates, Nikkel et al. reported a 22.5% 5-year fracture incidence (61). It is likely the benefit of ECSW regimens on fracture risk could potentially be greater if data on overall fracture incidence had been collected. Small bone peripheral and asymptomatic or minimally symptomatic vertebral fractures are the most common fractures in kidney transplant recipients managed with corticosteroids (2,61); such fractures would not have been captured by this analysis. It is also noteworthy that the reduction in incident fracture with ECSW was apparent within the first year and became significant within 2 years of transplantation. Elevated fracture risk occurs early after transplantation (3), with mean time to first fracture reported as early as 13 to 22 months (43,48,62) posttransplantation. This is in part related to severe bone loss in the first 6 months of transplantation associated with high dose of administered corticosteroid. Preservation of bone mass in the early, posttransplantation period by ECSW (19) may mechanistically account for lower fracture rates.

Although we reported ECSW is associated with the clinical benefit of lower posttransplantation fracture rates in comparison to CSBI, not all kidney transplant recipients are appropriate candidates for corticosteroid withdrawal (15). Furthermore, although a randomized trial of ECSW versus CSBI reported equivalent long-term graft function, the decision to manage patients with an ECSW regimen needs to consider potential morbidity associated with an increased risk of mild (Banff 1A) rejections, that are usually responsive to a short course of corticosteroids (16). Although we reported that 61 patients would need to be managed with ECSW to prevent one fracture, for every 14 patients managed with ECSW, there may be one additional rejection episode in comparison to CSBI (16). Indeed, in some patients corticosteroid immunosuppression may be unavoidable or its protective benefit on rejection may outweigh any associated risk of bone disease and fracture.

This study has limitations. This was not a randomized clinical trial and is subject to limitations of observational research using registry- and claims-based data. However,

relationships between immunosuppression type and fracture remained significant both after adjustment for multiple covariates that may affect fracture risk and in a propensity score analysis. Although UNOS follow-up of immunosuppression after transplantation was incomplete for the majority of patients, we adjusted risk models for the occurrence of rejection as a surrogate for corticosteroid initiation after transplantation. For patients initially discharged without corticosteroids, subsequent administration of corticosteroids would attenuate relationships reported by our intention-to-treat analysis; the protective benefit of withdrawal may be stronger than these data suggest. Regarding patients who may not be appropriate for corticosteroid withdrawal, we excluded any patient with a previous kidney or multiple organ transplant and we adjusted the multivariate model for a history of comorbid conditions that may require long-term corticosteroid use (nephritis and nephrosis). Finally, new onset posttransplantation diabetes (NO-DAT) is a common and important complication of immunosuppression and some studies suggested CS withdrawal was associated with decreased NODAT occurrence and severity (16,63). As our findings indicated that pretransplantation diabetes was associated with increased fracture risk, NODAT may also modify fracture risk after transplantation. However, we were unable to assess relationships between fracture and NODAT as we lacked sufficient claims data to validly identify NODAT incidence (63,64). Future investigations need to address the lack of published data regarding relationships between fracture and NODAT.

In conclusion, in patients discharged from the hospital after kidney transplantation without corticosteroids, there was a 31% decreased risk of fracture requiring hospitalization compared to those discharged on traditional corticosteroid-based regimens. These data provide more evidence that ECSW regimens may be clinically beneficial. Prospective studies are needed to evaluate both overall fracture rates, including vertebral fractures, among patients managed with ECSW and CSBI regimens, and the mechanisms by which these immunosuppression regimens affect bone quality and propensity for fracture.

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Abbreviations

BMD	bone mineral density
BMI	body mass index
CKD	chronic kidney disease
CMMS	Centers for Medicare and Medicaid Services
CSBI	corticosteroid-based immunosuppression
ECSW	early corticosteroid withdrawal
ESRD	end stage renal disease

ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IQR	interquartile range
UNOS	United Networks for Organ Sharing
US	United States
USRDS	United States Renal Data System

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Figure 1.
Kaplan–Meier plot of time to fracture resulting in hospitalization, stratified by immunosuppression regimen.

Figure 2.

Graphical representation of hazard ratios with 95% confidence intervals from the multiple proportional hazard regression model: The relative influence of risk factors for fracture on fracture risk after kidney transplantation.

Figure 3.

(A) Risk of posttransplantation fracture leading to hospitalization stratified by corticosteroid use for diabetic, white women with a history of pretransplantation dialysis; (B) risk of posttransplantation fracture leading to hospitalization stratified by corticosteroid use for nondiabetic, white women with a history of pretransplantation dialysis; (C) risk of posttransplantation fracture leading to hospitalization stratified by corticosteroid use for diabetic, white men with a history of pretransplantation dialysis; (D) risk of posttransplantation fracture leading to hospitalization stratified by corticosteroid use for nondiabetic, white men with a history of pretransplantation dialysis.

Table 1

Cohort characteristics for first-time kidney transplantation recipients, 2000–2006, stratified by corticosteroid use at hospital discharge

Variable	(n = 11 164)	(n = 66 266)	p-Value
Fracture			
Prekidney transplant (%)	1.4	1.3	NS
Postkidney transplant (%)	1.7	3.3	<0.001
Age at transplantation in years (SD)	49.9(13.4)	48.9(13.4)	<0.001
Female gender	38%	40%	<0.001
Race			
White	68.8%	65.3%	<0.001
Black	19.8%	25.1%	<0.001
Asian	3.7%	4.7%	<0.001
Other	7.7%	4.9%	<0.001
BMI in kg/m ² (SD)	27.5(5.7)	27.1(5.5)	<0.001
BMI < 18.5	2.6%	2.5%	NS
BMI 18.5–25	29.5%	30.0%	NS
BMI 25–30	29.8%	28.6%	.0170
BMI >30	27.5%	23.3%	<0.001
Missing	10.6%	15.5%	<0.001
Mean HLA-A, HLA-B and HLA-DR mismatches (SD)	2.2 (1.7)	2.3 (1.7)	0.02
0 mismatches (%)	15.9%	14.9%	0.007
1–2 mismatches (%)	41.8%	41.4%	NS
3–4 mismatches (%)	29.9%	30.9%	0.03
5–6 mismatches (%)	11.4%	11.1%	NS
Donor type (%)			<0.001
Living donor	49%	41%	
Deceased donor	51%	59%	
Induction	99.3%	83.0%	<0.001
Rejection (any vs. none)	8.6%	13.1%	<0.001
Pretransplant diabetes (recipient %)	33%	30%	<0.001
End-stage renal disease (%)			
Nephritis	17.6%	19.2%	<0.001
Nephrosis	7.2%	6.8%	0.06
Diabetes mellitus	26.0%	24.1%	<0.001
Hypertension	20.6%	21.8%	0.003
Tubulo-interstitial	16.0%	15.1%	0.01
Other	12.6%	13.1%	NS
Pretransplantation dialysis (%)	78.5%	82.0%	<0.001
Parathyroidectomy (%)			
Pretransplant	1.8%	2.5%	<0.001
Posttransplant	1.0%	2.0%	<0.001

Variable	(n = 11 164)	(n = 66 266)	p-Value
Year of transplant			<0.001
2000	2.4%	97.6%	
2001	4.2%	95.8%	
2002	5.8%	94.2%	
2003	11.5%	88.5%	
2004	20.0%	80.0%	
2005	23.9%	76.1%	
2006	32.2%	67.8%	

Table 2

Multivariate Cox regression model of risk of fracture after kidney transplantation

Variable	Hazard ratio (HR)	95% Confidence intervals		p-Value
Corticosteroid at hospital discharge				
Steroid-based	(Reference)			
Steroid-withdrawal	0.69	0.59	0.81	<0.001
Age at transplantation				
18–50	(Reference)			
50–65	1.76	1.59	1.94	<0.001
>65	3.27	2.91	3.67	<0.001
Gender				
Male	(Reference)			
Female	1.42	1.31	1.55	<0.001
Race				
White	(Reference)			
Black	0.63	0.56	0.70	<0.001
Asian	0.34	0.26	0.47	<0.001
Other	0.89	0.73	1.09	NS
BMI (kg/m ²)				
BMI < 18	1.39	1.08	1.78	0.01
BMI 18–25	(Reference)			
BMI 25–30	0.87	0.78	0.96	0.008
BMI > 30	0.83	0.75	0.93	0.002
HLA-A, HLA-B and HLA-DR mismatches				
0 mismatches	(Reference)			
1–2 mismatches	1.01	0.89	1.14	NS
3–4 mismatches	1.03	0.90	1.17	NS
5–6 mismatches	1.07	0.93	1.25	NS
Donor type				
Living donor	(Reference)			
Deceased donor	1.36	1.24	1.49	<0.001
Rejection (any vs. none)	1.10	0.98	1.23	NS
Pretransplant fracture ^I	2.82	2.33	3.43	<0.001
Pretransplant diabetes (recipient)	2.05	1.76	2.39	<0.001
Cause of end stage renal disease				
Nephritis	0.85	0.73	1.00	0.05
Nephrosis	0.73	0.57	0.93	0.01
Diabetes mellitus	1.39	1.18	1.64	<0.001
Hypertension	(Reference)			
Tubulo-interstitial	0.89	0.76	1.05	NS
Other	0.94	0.80	1.11	NS
Pretransplant dialysis	1.56	1.36	1.77	<0.001

Variable	Hazard ratio (HR)	95% Confidence intervals		p-Value
Year of transplant				
2000	(Reference)			
2001	1.11	0.97	1.26	NS
2002	1.10	0.96	1.26	NS
2003	1.08	0.93	1.25	NS
2004	1.09	0.93	1.28	NS
2005	1.15	0.97	1.37	NS
2006	1.10	0.89	1.35	NS

¹ Between time of ESRD listing and transplant.