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Pancreas-kidney transplantation is associated with reduced fracture risk compared to kidney alone transplantation in men with type 1 diabetes

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Abstract

Both type 1 diabetes mellitus and end stage renal disease are associated with increased fracture risk, likely due to metabolic abnormalities that reduce bone strength. Simultaneous pancreas-kidney transplantation is a treatment of choice for patients with both disorders, yet the effects of simultaneous pancreas-kidney versus kidney transplantation alone on post-transplantation fracture risk are unknown. From the United States Renal Data System we identified 11, 145 adults with type 1 diabetes undergoing transplantation of whom 4,933 had a simultaneous pancreas-kidney while 6, 212 had a kidney alone transplant between 2000 and 2006. Post-transplantation fractures resulting in hospitalization were identified from discharge codes. Time to first fracture was modeled and propensity score adjustment was used to balance covariates between groups. Fractures occurred in significantly fewer (4.7%) of pancreas-kidney compared to kidney-alone transplant (5.9%) cohorts. After gender stratification and adjustment for fracture covariates, pancreas-kidney transplantation was associated with a significant 31% reduction in fracture risk in men (hazard risk 0.69). Older age, white race, prior dialysis and pre transplantation fracture were also associated with increased fracture risk. Prospective studies are needed to determine the gender-specific mechanisms by which pancreas-kidney transplantation reduces fracture risk in men.

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Keywords

pancreas-kidney transplantation; fracture; kidney; diabetes; renal; gender differences; USRDS

Introduction

Fractures are common after kidney transplantation. In comparison to the general population, fracture risk is more than 3-fold higher [1–4] and in comparison to patients on hemodialysis, hip fracture risk is more than 30% higher [1]. Unfortunately, therapeutic agents that have been demonstrated to prevent fracture due to either post-menopausal or glucocorticoid-induced osteoporosis have not been proven effective in kidney transplant recipients [5]. Indeed, while small clinical trials have demonstrated that anti-resorptives, calcium and vitamin D prevent bone loss after kidney transplantation, reduction in fracture risk has not been clearly deomonstrated [5]. Although the lack of efficacy of these fracture preventative agents is very likely an artifact of inadequately powered clinical trials, it remains concerning that definitive therapeutic strategies to prevent fractures are lacking for kidney transplant recipients in light of their 60% increased mortality risk after hip fracture in comparison to the general population [6]. Therefore, there is urgent need to identify and study novel strategies that lower fracture risk in the more than 170,000 kidney transplant recipients that are living in the United States (U.S.) [7].

Epidemiologic studies have reported that type 1 diabetes mellitus (T1DM) increases fracture risk in patients with [8] and without [9–11] kidney transplantation. Indeed, our group [12, 13] and others [4, 14, 15] have shown that pre-transplantation diabetes more than doubles the risk of fractures after kidney transplantation. The mechanisms by which T1DM increases fracture risk are not completely understood, but may include low bone mineral density [10, 16, 17], low circulating levels of insulin like growth factor1 (IGF-1) [18], decreased bone formation rates [19], elevated glucose levels [20], the development of altered collagen structure due to the accumulation of advanced glycation end products [21–23], micro-vascular complications [9, 24, 25] and an increased risk of falls due to peripheral neuropathy. It is not known whether correction of T1DM by pancreas transplantation decreases fracture risk.

Simultaneous pancreas-kidney transplantation is the treatment of choice for patients with end stage renal disease (ESRD) and T1DM [26]. While animal [27] and human [28, 29] data suggest that exogenous insulin administration may correct abnormal bone and mineral metabolism due to T1DM, other data suggest that exogenous insulin may increase fracture risk [24, 28, 30] as a complication of hypoglycemia associated falls.

However, simultaneous pancreas-kidney transplantation provides physiologic-type insulin repletion without the hypoglycemic consequences of exogenous insulin administration [31]. Moreover, in patients with T1DM and ESRD, simultaneous pancreas-kidney transplantation provides superior clinical outcomes compared to kidney transplantation alone [32], including normalized levels of insulin and glucose [32], improvements in micro- and macro-vascular complications [33, 34], prevention of diabetic nephropathy [31] and stabilization of diabetic neuropathy [35]. Therefore, based on data suggesting that the adverse metabolic and clinical outcomes associated with T1DM are improved by pancreas-kidney transplantation, we

hypothesized that in patients with T1DM and ESRD, simultaneous pancreas-kidney transplantation would be associated with lower fracture risk than kidney transplantation alone. To test our hypothesis, we used the United States Renal Data System (USRDS), the largest U.S. kidney and pancreas transplantation database.

Materials and Methods

Patients

The USRDS is the largest registry of kidney transplantation recipients and combines the United Networks for Organ Sharing (UNOS) transplantation registry data with payment data from the Centers for Medicare and Medicaid Services, which is the primary payer for the majority of patients with ESRD [36, 37]. We used the USRDS data to estimate the incidence of fractures resulting in hospitalization among patients with T1DM undergoing either simultaneous pancreas-kidney or kidney transplantation alone between January 1, 2000 and December 31, 2006. Diabetes type was determined by the primary patient diagnosis reported on UNOS forms and included in the USRDS database. Patients were excluded from this analysis for: age less than 18 years; transplantation occurring prior to 2000; a history of multiple kidney or other organ transplantations; residence in an institution; being unable to ambulate; and requiring assistance with activities of daily living. We did not exclude patients who received a living donor kidney because in a sensitivity analysis including only patients with a deceased donor kidney the hazard ratio (HR) was materially unchanged from that of entire cohort (HR 0.70; 95% CI 0.55–0.89).

Determination of Date of First Fracture

First-time fracture events 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. 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 the first listing of a fracture specific ICD-9-CM code as the fracture event. Both traumatic and fragility fractures were included. An analysis excluding traumatic fractures was not conducted because the severity of trauma associated with fracture was not completely recorded in USRDS. However, similar to low-trauma fractures, high-trauma fractures are associated with low-bone mineral density (BMD) and increased risk of future fracture [38].

Ascertainment of Fracture Covariates

Data on fracture covariates were obtained from the USRDS, selected on the basis of epidemiologic studies that demonstrated their ability to predict fracture risk in the general, chronic kidney disease (CKD) and kidney transplant populations [1, 2, 39–43]. These included age at transplantation (years), gender, race (White, Black, Asian and other), body mass index (BMI), human leukocyte antigen (HLA)-matching (0; 1–2; 3–4; and 5–6), a history of and length of pre-transplantation dialysis and a history of prior fracture. BMI was evaluated both as continuous and categorical parameters: underweight (BMI <18.5), normal (BMI between 18.5 and 24.9), overweight (BMI between 25 and 29.9), and obese (BMI of >30). BMI >50 (n = 20) was considered a measurement error and was classified along with those

missing BMI measurements (n = 1513 patients). A history of pre-transplantation fracture was determined by the presence of an ICD-9-CM fracture code with a date of service prior to transplant.

Statistical Analysis

All analyses were performed using STATA (version 8.2; StataCorp LP, College Station, TX) and SAS (v9.2, Gary, NC) statistical software. Analyses were designed to: (1) compare characteristics of T1DM patients with either a first kidney or simultaneous pancreas-kidney transplant; (2) quantify fracture risk by transplant type while controlling for fracture covariates; and (3) evaluate time to first fracture controlling for patient and transplant characteristics. Categorical parameters were compared using chi-square tests and continuous parameters were compared using Student's t tests. Time to first fracture was modeled using the Kaplan-Meier method with comparisons made between strata with the log-rank test. Proportional hazard regression was used to quantify fracture risk of simultaneous kidney-pancreas transplantation in comparison to kidney transplantation alone, while adjusting for predefined covariates of fracture determined from univariate analyses. Finally, due to the observational nature of this investigation, multiple fracture covariates were unequally distributed between transplantation groups, potentially favoring a fracture reduction benefit in pancreas-kidney recipients. Therefore, propensity scores were created for the probability of receiving a pancreas-kidney versus kidney transplant [44]. Covariates included in the propensity score model included demographic and co-morbidity characteristics. The multivariable proportional hazard regression model included the predictor of interest (simultaneous pancreas-kidney versus kidney alone) adjusted for the propensity score.

Results

Cohort Characteristics

Using the USRDS, 11,145 adults with a primary diagnosis of T1DM were identified who underwent either simultaneous pancreas-kidney (N = 4,933) or kidney (N = 6,212) transplantation between January 1, 2000 and December 31, 2006. Patient survival rates after transplantation with either a pancreas-kidney or a kidney alone were similar at one year (95.1% versus 94.8%, respectively; p-value NS) but superior for pancreas-kidney at both three (90.7% vs. 87.8%; p-value < 0.001) and five years (86.0% vs. 79.6%; p-value < 0.0001). There were small but significant differences between patients transplanted with a pancreas-kidney and a kidney alone (Table 1). Although transplant recipients in both groups were young, patients who received a pancreas-kidney were 5.6 years younger on average than patients who received a kidney alone (p-value < 0.0001). In addition, patients with a simultaneous pancreas-kidney transplant had slightly lower BMI, were more likely to be male or white, had fewer HLA mismatches and although they were slightly more likely to have received dialysis, they were on dialysis for less time. Between-group differences in glucocorticoid use were small and not significant. There was no difference in the prevalence of pre-transplantation fractures.

Cumulative Incidence and type of hospitalization-associated fractures according to type of transplantation

The cumulative incidence of fractures leading to hospitalizations during follow-up was slightly but significantly lower for patients transplanted with a pancreas-kidney than a kidney alone (4.7% vs. 5.9%, respectively, p-value 0.005); the absolute risk reduction was 1.2 percentage points. Out of all fractures, the most common sites were femur (25%), ankle (16%) and tibia/fibula (13%). Fractures of the hip, pelvis and humerus were significantly less common after transplantation with a pancreas-kidney than a kidney alone (Hip: 0.8% versus 1.3%, respectively, p-value 0.01; Pelvis: 0.2% versus 0.5%, respectively, p-value 0.01; and Humerus: 0.3% versus 0.6%, respectively, p-value 0.03).

Risk of fractures leading to hospitalization according to type of transplantation

Five-hundred ninety four fractures resulting in hospitalizations were indentified over 42,755 patient-years of follow-up. For patients transplanted with a simultaneous pancreas-kidney and kidney alone, median (interquartile range) follow-up was 3.8 (2.1 – 5.8) and 3.5 (2.0 – 5.4) years, respectively. Incidence rates of fracture per 1000 patient-years for patients who received a pancreas-kidney or kidney alone were 11.7 and 15.7, respectively (Figure 1). Fracture incidence rates adjusted for patient-years of follow-up at all anatomic sites and stratified by type of transplantation are shown in Figure 2.

Fracture free survival was determined by the Kaplan-Meier method (Figure 3). At three months after transplantation, fracture incidence rates began to differ between groups; there were fewer fractures among patients with T1DM who received a simultaneous pancreas-kidney, compared to kidney alone. The beneficial effect of transplantation with a pancreas-kidney compared to kidney alone on fracture risk persisted for the duration of follow-up (p-value <0.0003).

In univariate hazard regression analysis, pancreas-kidney transplantation, compared to kidney transplantation, was protective against fractures in general (HR 0.74; 95% CI 0.63–0.88) and at the hip (HR 0.59; 95% CI 0.42–0.82), pelvis (HR 0.38; 95% CI 0.19–0.78) and humerus (HR 0.45; 95% CI 0.24–0.85). However, in multivariable analysis, pancreas-kidney transplantation was protective against fractures in general (HR 0.79; 95% CI 0.66–0.96) and at the pelvis (HR 0.46; 95% CI 0.21–1.00). While black race was also protective against fractures (HR 0.76; 95% CI 0.57–0.99), older age (HR 1.02; 95% CI 1.01–1.03), BMI <18.5 kg/m^2 (HR 1.91; 95% CI 1.25–2.94) and both pre-transplantation fracture (HR 3.58; 95% CI 2.53–5.07) and dialysis (HR 1.48; 95% CI 1.18–1.86) were associated with increased fracture risk.

Gender specific associations between fracture risk and simultaneous pancreas-kidney transplantation

Female gender is an important risk factor for fracture after kidney transplantation[4, 12–14]. A test of interaction between gender and pancreas-kidney transplantation was near-significant (HR 1.39; 95% CI 0.98–1.96, p-value 0.06). Therefore, we evaluated gender-specific effects on post-transplantation fracture (Table 2). In men with T1DM, simultaneous pancreas-kidney transplantation was associated with a 31% reduction in overall fracture risk (HR

0.69; 95% CI 0.53–0.88). Higher BMI (>25 kg/m^2) was also associated with reduced fracture risk (BMI 25–30 kg/m^2 HR 0.75; 95% CI 0.58–0.97 and BMI 30–50 HR 0.62; 95% CI 0.43–0.90). For pelvic fractures in men, pancreas-kidney transplantation was associated with a 91% risk reduction (HR 0.09; 95% CI 0.01–0.71). In women, simultaneous pancreas-kidney transplantation was not associated with decreased fracture risk. To evaluate the potential influence of menopausal status on fracture risk we stratified the female population by age 50 years; there was no fracture prevention benefit to pancreas-kidney transplantation in either younger or older women. Black race was protective against fractures in women (HR 0.52; 95% CI 0.33–0.81). Older age, lower BMI (<18.5 kg/m^2) and both pre-transplantation fracture and dialysis were all independent predictors of increased fracture risk in both men and women.

Propensity score adjustment of hazard regression models

Imbalances in the distribution of fracture risk factors between transplantation groups may have biased results in favor of pancreas-kidney recipients. Therefore, we used propensity score models to confirm the validity of our findings in both the whole and gender stratified cohorts. In the whole cohort, there was a 21% reduction in all fractures (HR 0.79; 95% CI 0.65–0.95) and a 58% reduction in pelvic fractures (HR 0.42; 98% CI 0.19–0.94). In men, there was a 33% reduction in all fractures (HR 0.67; 95% CI 0.52–0.86) and a 92% reduction in pelvic fractures (HR 0.08; 98% CI 0.01–0.63). There was no reduction in hip fracture rates in the whole cohort, but in men there was a trend towards a 39% reduction in risk (HR 0.61; 95% CI 0.38–1.00, p-value 0.054). Similar to models unadjusted for propensity score, there was no association between fracture and transplant type in women.

Discussion

These results are the first to show that fracture rates in patients with T1DM are lower after transplantation with a simultaneous pancreas-kidney compared to kidney alone. In men with T1DM and ESRD, the benefit of simultaneous pancreas-kidney transplantation was independent of other risk factors for fracture and was apparent within three months of transplantation. Over five years, the incidence of fracture was 31% lower in men but not significantly different in women. We also noted that transplantation with a simultaneous pancreas-kidney was associated with a reduction in pelvic fractures and a trend towards a reduction in hip fractures compared to a kidney alone. In light of the 60% increased mortality risk[6] and the substantially increased health economic costs[45, 46] that are associated with fractures after kidney transplantation, simultaneous pancreas-kidney transplantation confers a clinically important fracture prevention benefit to this group of young men. These results are even more striking considering that no single treatment has been proven to be effective for reducing fracture risk after kidney transplantation.

We reported that the incidence of fractures resulting in hospitalizations was 12.0 and 15.8 per 1000 patient-years for patients transplanted with either a pancreas-kidney or kidney alone. This advantageous effect of pancreas-kidney transplantation contrasts with previously published data. Ramsey-Goldman et al[3] noted higher percentages of men, women and postmenopausal women with fractures among those who received a pancreas-kidney

compared to a kidney alone. A retrospective cohort study by Chiu et al[47] demonstrated a significantly increased risk of fracture after simultaneous pancreas-kidney transplantation compared with kidney transplantation. Likewise, Vautour et al[4] found that pancreas-kidney transplantation was associated with increased fracture risk. It is important to note that the control groups in all these studies were not well matched to the pancreas-kidney groups. In particular, patients were not matched on either T1DM status, which is itself an extremely important risk factor for fracture[12, 13] or race[47], which in the case of blacks confers a fracture prevention benefit. In fact, ours is the only study with sufficient power both to match patients with and without pancreas transplantation based on T1DM status and to perform analyses that were adjusted for multiple confounders of fracture risk. Therefore, our comparisons more clearly reflect the effects of pancreas transplantation on fracture risk.

Our results also suggest that the fracture reduction benefits of simultaneous pancreas-kidney transplantation apply to men but not women. Gender specific differences in rates of bone loss after kidney transplantation have been reported[48–54]. Male gender was noted to be a significant risk factor for low bone mineral density after kidney transplantation[51]. Other studies also suggest that female gender was protective against bone loss at the lumbar spine[49, 50] and femoral neck[52, 53] after kidney transplantation. Indeed, higher levels of circulating estrogen correlated with less severe bone loss at the lumbar spine[49] and with histologic markers of bone structure and osteoblast function[51]. In our USRDS analysis, 75% of the women who received a pancreas-kidney from January 1, 2000 to December 31, 2006 were younger than 50 years of age and the majority of these women were likely premenopausal. Therefore, it is possible that the skeletal effects of pancreas-kidney transplantation in women were attenuated because they were estrogen replete. However, in gender- and age-stratified statistical analyses, we did not find any fracture prevention benefit in older women. Furthermore, these findings may have been influenced by our inability to ascertain and quantify the effects of medications that have active bone affects, such as oral contraceptives, hormone replacement therapy, vitamin D and calcium supplements and bisphosphonates, all of which are more commonly used by women. Further investigations are needed to explore the microstructural and biochemical mechanisms of fracture that underlie these gender differences.

T1DM is an important risk factor for fracture both in the general population[9, 28] and in patients with chronic kidney disease (CKD) both before[9] and after[8] kidney transplantation. In this study we report an overall fracture incidence rate of 14.0 per 1000 patient-years, which is markedly higher than the rate of fractures in kidney transplant recipients without diabetes (7.2 per 1000 patient-years). Furthermore, we reported previously that kidney transplant recipients with diabetes, compared to non-diabetics, had a more than 2-fold increased risk of fractures requiring hospitalization, regardless of age, gender, pre-transplantation dialysis and immunosuppression regimen[13]. Mechanisms of fracture due to T1DM are not fully understood. A recent study of patients with T1DM, without either renal disease or micro-vascular complications, suggested there was no difference in bone mass, microstructure or remodeling in comparison to healthy controls[55]. However, in other cohorts, T1DM was associated with low BMD[10, 16, 17]. This may have been due to low levels of circulating IGF-1[18], decreased bone formation rates[19], elevated blood glucose levels[20], abnormal mineralization due to altered collagen structure from advanced glycation

end products[21, 22], poor bone blood flow from micro-vascular complications[9, 24, 25], endothelial cell dysfunction[56] or peripheral neuropathy[57]. In addition, hypoglycemic events due to exogenous administration of insulin have been implicated as a cause of falls which in turn, may result in fracture[28, 30]. It is also important to note that mechanisms of increased fracture risk in patients with co-incident T1DM and CKD have not been fully explored. CKD is an important diabetic complication that is independently associated with an increased risk of fracture. Compared to the general population, CKD is associated with a 2- to 4- fold increased risk of fracture[1, 2, 40, 58–60] and compared to patients with T1DM alone, co-incident T1DM and CKD has been reported to increase fracture risk 40%[9] to 42-fold[17]. Studies are needed to clarify mechanisms of fracture in patients with co-incident T1DM and CKD in order to develop effective fracture prevention strategies that can be used in conjunction with pancreas-kidney transplantation in men and to provide fracture prevention therapies to women in whom pancreas transplantation may offer no fracture reduction benefit at all.

Although we found that pancreas-kidney transplantation conferred a fracture reduction benefit compared to kidney transplantation alone, fractures continued to occur even after dual organ transplantation. Potential mechanisms of increased skeletal fragility after simultaneous pancreas-kidney transplantation have been reported in several small investigations[61–63]. Both pre- and post- transplantation characteristics of the skeleton had important implications for future fracture risk. Before transplantation, up to 58% and 23% of patients with T1DM and ESRD had osteoporosis at the femoral neck and lumbar spine, respectively[61, 62]. In patients with kidney transplantation, glucocorticoid use is an important risk factor for fracture[13]. During the first six months after transplantation, reported rates of bone loss were 6.9% and 6% at the femoral neck and spine, respectively, possibly due to the high doses of glucocorticoids used during that time period. After glucocorticoid doses were lowered, bone density did not recover and remained significantly below pre-transplantation levels[61]. The pattern of bone loss after pancreas-kidney transplantation was predominantly cortical[63], which may explain the strong association between pancreas-kidney transplantation and peripheral fractures[47, 61, 62, 64].

Unfortunately, no study has evaluated whether the rates and patterns of bone loss after pancreas-kidney transplantation are due to effects of either dual organ transplantation or T1DM. Simultaneous pancreas-kidney transplantation results in the correction of pre-transplantation metabolic derangements. This includes normalized regulation of serum glucose, phosphate and calcium, restored secretion of calcitriol, reversal of pre-transplantation hyperparathyroidism and improvement in micro-vascular disease[50, 65]. We hypothesize that the reversal of these derangements after simultaneous pancreas-kidney transplantation may account for some of the beneficial effects on fracture risk.

Finally, an uneven distribution of fracture risk factors between transplant recipients may have biased the unadjusted risk estimates of fracture in favor of the pancreas-kidney group. For example, recipients of a kidney alone had a longer mean duration of pre-transplantation dialysis, were commonly older and female and had a greater prevalence of HLA mismatches and pre-transplantation parathyroidectomy. On the other hand, other risk factors for fracture were more common in recipients of pancreas-kidney transplantation; all recipients of a

pancreas-kidney received a deceased donor transplant and they were more likely to be white, of lower BMI and to have received pre-transplantation dialysis. Although, these data suggest recipients of a pancreas-kidney may have been healthier than those of a kidney alone, we *a priori* excluded debilitated patients, including those with an inability to ambulate, requiring assistance and residing in a facility. These imbalances in the distribution of fracture risk factors between transplantation groups are an important limitation of this study and were addressed in two separate analyses. First, all multivariable analyses were adjusted for known independent predictors of post-transplantation fracture. Second, a propensity score approach was used as a statistical method to balance inequalities in covariate structure[44]. The results of both analytical methods were consistent with each other, indicating a fracture prevention benefit of pancreas-kidney transplantation in men. Therefore, we believe these adjustments limited bias in fracture risk estimates.

This study also has other limitations. It was not a randomized clinical trial and is subject to the limitations of observational research using registry and claims based data. However, the reduced fracture risk after transplantation with a pancreas-kidney compared to a kidney alone was significant both after adjustment for other risk factors for fracture and after the use of propensity scores. If this were a randomized clinical trial, an absolute fracture risk reduction of 1.8 percentage points in men would equate with the prevention of one incident fracture requiring hospitalization for every 56 male patients receiving a simultaneous pancreas-kidney. Therefore, in the 3670 male patients in this study who received a kidney alone, 65 fractures would have been prevented if a pancreas had also been transplanted. As fractures were assessed by ICD9 hospital codes, we were limited to fractures resulting in hospitalization. This almost certainly led to under-detection of smaller peripheral fractures and morphometric vertebral fractures; however, our analysis did identify those fractures that were the most clinically significant. The USRDS does not contain information on either bone mineral density or medication usage after hospital discharge. However, the role of low bone mineral density as a risk factor for fracture in patients with ESRD has not been fully elucidated. Regarding medication usage, we were unable to control for the impact of chronic glucocorticoid and calcineurin inhibitor use on fracture rates. However, multivariable models and propensity scores included surrogate markers of glucocorticoid use, including hospital discharge with a glucocorticoid and a history of graft rejection. Finally, we were unable to differentiate simultaneous pancreas-kidney from simultaneous cadaver pancreas living-donor kidney transplantation and determine if there are differences in fracture risk between these two transplantation approaches.

In conclusion, simultaneous pancreas-kidney transplantation compared to kidney transplantation alone was associated with a 31% reduction in overall fracture risk along with a significant reduction in pelvic fracture risk and a trend towards reduced hip fracture risk in men with T1DM and ESRD. Long-term prospective mechanistic studies are needed to elucidate the effects of T1DM and gender on fracture risk after pancreas-kidney and kidney transplantation so that effective fracture prevention strategies can be developed and implemented.

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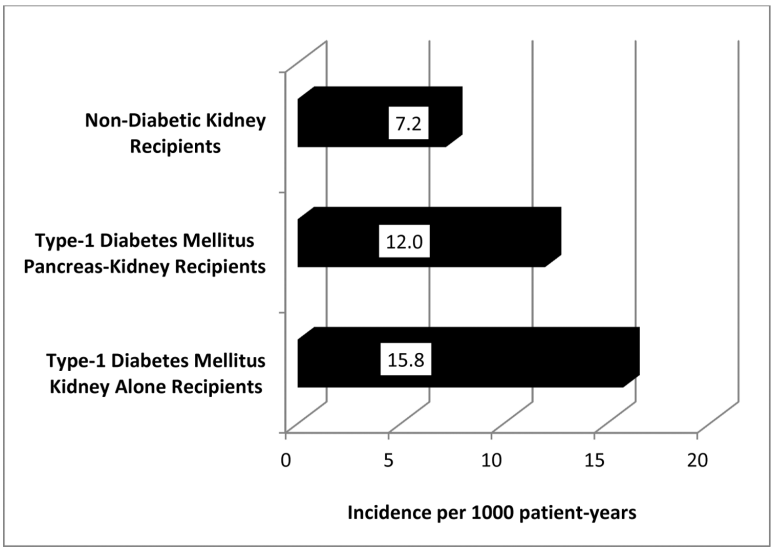

Figure 1.
Fracture incidence per 1000 patients per year by transplant type

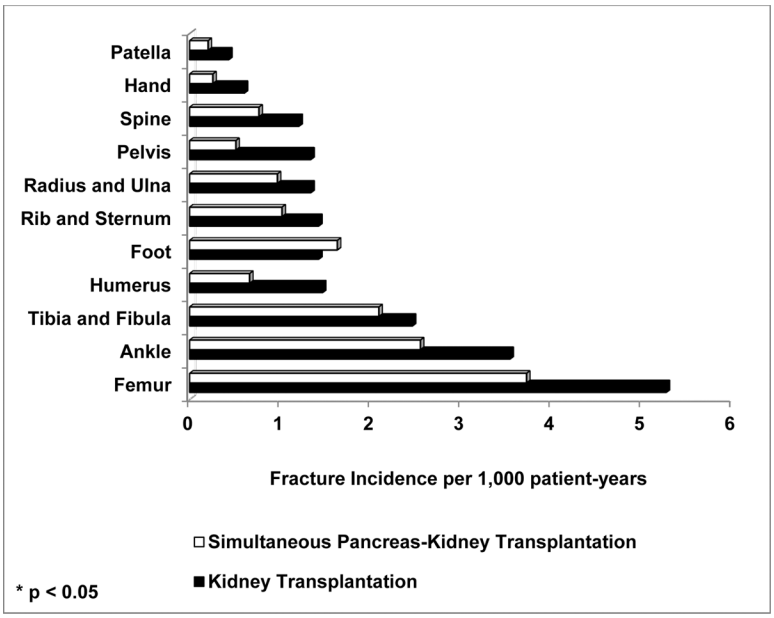

Figure 2.
Fracture incidence per 1000 patients per year at each skeletal site by transplant type

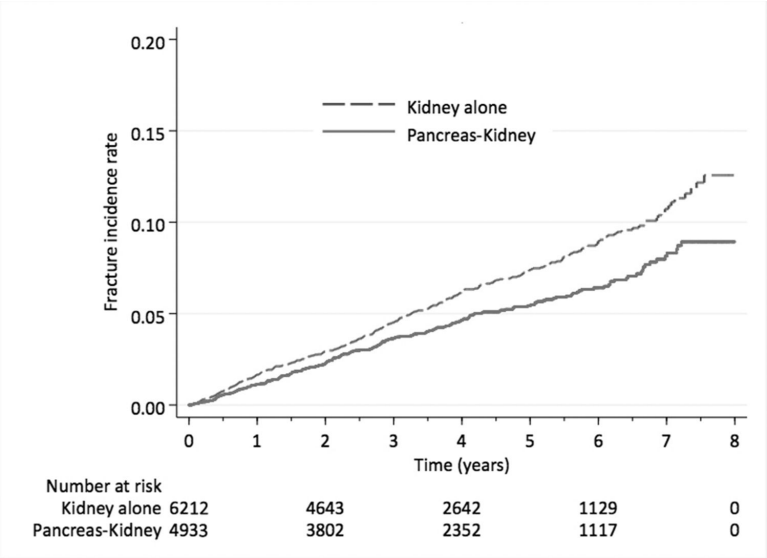

Figure 3.

Kaplan-Meier plot of time to fracture resulting in hospitalization, stratified by kidney transplant type.

Table 1

Characteristics: Patients with Type 1 Diabetes Mellitus Stratified by Transplant Type

Variable	Kidney Transplantation (n = 6212)	Simultaneous Pancreas-Kidney Transplantation (n = 4933)	P value
Pre-Transplantation Fracture (%)	2.2	1.8	0.1
Age at transplantation in years (SD)	46.0 (10.9)	40.4 (8.1)	<0.0001
Female Gender (%)	41	39	0.02
Race (%)			
White	79.3	83.7	<0.0001
Black	14.7	12.7	0.002
Asian	1.3	0.8	0.02
Other	4.7	2.7	<0.0001
BMI in kg/m^2 (SD)	26.7 (5.6)	24.8 (5.7)	<0.0001
BMI < 18.5(%)	1.9	2.5	0.03
BMI 18.5–24.9 (%)	34.0	47.7	<0.0001
BMI 25–30 (%)	29.5	28.4	0.2
BMI 30–50 (%)	19.9	9.1	<0.0001
Missing (%)	14.7	12.4	<0.0001
Mean HLA-A, HLA-B, and HLA-DR mismatches (SD)	2.4 (1.7)	1.3 (1.2)	<0.0001
0 mismatches (%)	14.2	26.8	<0.0001
1–2 mismatches (%)	38.2	59.2	<0.0001
3–4 mismatches (%)	32.7	11.1	<0.0001
5–6 mismatches (%)	13.8	1.8	<0.0001
Deceased Donor (%)	48	100	<0.0001
Pre-Transplant Dialysis (%)	78.4	80.9	0.001
Years on Pre-Transplant Dialysis (SD)	2.4 (2.1)	2.0 (1.7)	<0.0001
Parathyroidectomy (%)	1.8	1.0	<0.0001
Corticosteroid Maintenance Immunosuppression (%)	79.6	80.0	0.6
Year of Transplant - Number (%)			
2000	835 (53.5)	725 (46.5)	
2001	895 (55.6)	715 (44.4)	
2002	941 (57.5)	696 (42.5)	
2003	821 (55.4)	660 (44.6)	
2004	992 (59.0)	688 (41.0)	
2005	894 (55.3)	723 (44.7)	
2006	834 (53.5)	726 (46.5)	

Table 2

Multivariable Hazard Ratios: Patients with Type 1 Diabetes who received either Kidney or Simultaneous Pancreas-Kidney Transplantation

	Men (N=6690)				Women (N=4455)			
	Hazard Ratio	**95% CI**		**P-value**	**Hazard Ratio**	**95% CI**		**P-value**
Simultaneous Pancreas-Kidney Transplantation	0.69	0.53	0.88	0.003	0.95	0.71	1.26	0.7
Pre-KTx Fracture	4.13	2.64	6.45	<0.0001	2.62	1.48	4.63	0.0009
Age at transplantation (per year over 18)	1.01	1.00	1.03	0.02	1.03	1.02	1.05	<0.0001
Race				-				
White		Reference				Reference		
Black	0.94	0.67	1.33	0.9	0.52	0.33	0.81	0.004
Asian	0.52	0.13	2.08	0.5	-	-	-	-
Other	0.96	0.51	1.83	0.9	0.91	0.42	1.96	0.8
BMI in kg/m^2				-				
BMI < 18.5	2.08	1.12	3.86	0.02	1.79	0.98	3.27	0.06
BMI 18.5–24.9		Reference				Reference		
BMI 25–30	0.75	0.58	0.97	0.03	1.09	0.79	1.49	0.6
BMI > 30–50	0.62	0.43	0.90	0.01	1.02	0.70	1.48	0.9
Missing	0.79	0.56	1.11	0.2	1.20	0.82	1.76	0.3
Mean HLA-A, HLA-B, and HLA-DR mismatches (SD)				-				
0 mismatches		Reference				Reference		
1–2 mismatches	0.98	0.73	1.32	0.9	1.17	0.83	1.64	0.4
3–4 mismatches	1.13	0.82	1.57	0.5	0.93	0.62	1.40	0.7
5–6 mismatches	1.09	0.71	1.68	0.7	1.00	0.61	1.64	1.0
Pre-Transplant Dialysis	1.39	1.02	1.88	0.04	1.64	1.17	2.31	0.005
Parathvroidectomy				-				
Pre- or Post-Transplant	0.32	0.04	2.26	0.6	1.33	0.88	3.03	0.5
Corticosteroid Maintenance Immunosuppression	1.08	0.76	1.54	0.7	0.81	0.56	1.17	0.3

	Men (N=6690)				Women (N=4455)			
	Hazard Ratio	**95% CI**		**P-value**	**Hazard Ratio**	**95% CI**		**P-value**
Year				-				
2000	Reference				Reference			
2001	1.39	0.99	1.96	0.06	1.24	0.85	1.81	0.3
2002	0.93	0.63	1.38	0.7	1.09	0.72	1.65	0.7
2003	1.28	0.87	1.90	0.2	1.00	0.63	1.58	1.0
2004	1.15	0.75	1.77	0.5	0.87	0.53	1.43	0.6
2005	1.12	0.69	1.83	0.6	0.82	0.46	1.45	0.5
2006	1.60	0.93	2.76	0.09	1.00	0.51	1.93	1.0