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Choices in kidney transplantation in type 1 diabetes: Are there skeletal benefits of the endocrine pancreas?

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Abstract

Traditionally, recipients of a simultaneous pancreas-kidney (SPK) versus kidney transplant alone (KTA) were thought to have higher fracture risk. Using a large US registry, Nikkel *et al* observed lower rates of fracture hospitalization among patients with type 1 diabetes after SPK compared to KTA, particularly among men. It is not known whether the apparent benefit of SPK is due to improved bone strength or fewer falls, but these findings may influence transplant decision making.

Long term patient and kidney allograft survival after kidney alone or simultaneous pancreas-kidney transplant in patients with type 1 diabetes are similar.[1] The choice between these strategies is often individualized and may be based on their expected impact on morbidity, in conjunction with other preference-based factors, such as wait time and the availability of living donors. Fractures are common after transplantation[2] and result in a substantial burden of disability.[3] This may be particularly relevant to patients with type 1 diabetes because of further elevation in fracture risk as a result of diabetes.[4] Despite this, few studies have specifically evaluated the risk of fracture in patients with type 1 diabetes after kidney transplantation.

The risk of fracture in this population is complex and related to the cumulative exposure to multiple factors that affect bone strength and risk of falls, including type 1 diabetes, advanced kidney disease and transplantation (Figure). Insulin itself has anabolic effects on bone, such that hypoinsulinemia in type 1 diabetes may impair bone strength. Furthermore, advanced glycation end products resulting from hyperglycemia accumulate in collagen where they may decrease bone strength by interfering with collagen cross-linking or by altering bone metabolism. Finally, common diabetic complications, such as peripheral neuropathy, autonomic neuropathy with orthostasis, visual impairment, amputation and episodes of hypoglycemia, result in postural instability that increase fracture risk even without affecting bone strength per se.[4] Advanced kidney disease confers additional fracture

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Disclosure

None.

risk due to high rates of secondary hyperparathyroidism, adynamic bone disease and osteomalacia.[2, 5] The risk of fracture escalates further after transplantation,[2] with the largest loss of bone mineral density in the first 12 months post-transplantation, possibly due to high doses of glucocorticoids, urinary phosphate wasting as a result of persistent elevation of parathyroid hormone and fibroblast growth factor 23, and post-operative immobilization.[6]

In the study by Nikkel *et al* in this issue of Kidney International,[7] the authors hypothesized that transplantation with a simultaneous pancreas-kidney, in lieu of a kidney transplant alone, would reduce the risk of post-transplant fracture in patients with type 1 diabetes by mitigating the impact of diabetes on fracture risk. They evaluated the rate of hospitalization for fracture among 6,212 patients with type 1 diabetes that received a kidney transplant alone compared to 4,933 patients that received a simultaneous pancreas-kidney transplant between 2000 and 2006 in the United States (US). Using Medicare billing data captured in the United States Renal Data System (USRDS), a national registry of patients with end-stage renal disease in the US, the authors ascertained 594 hospitalizations for fractures over a median follow-up of up to 3.8 years. They found that the rate of hospitalization for fracture was significantly greater after kidney alone compared with simultaneous pancreas-kidney transplant and that this difference persisted after adjustment for many fracture risk factors.

The use of a large administrative dataset, such as the USRDS, has the advantage of wide generalizability to the US transplant experience and provides the power to detect even relatively small effects on meaningful clinical outcomes. However, several disadvantages also require discussion. First and foremost is the lack of detailed information about how the two groups differed prior to transplantation. The authors excluded patients with significant functional impairment, including institutionalization and inability to ambulate or perform activities of daily living. Additionally, they ascertained important fracture covariates to the extent possible, including demographics, history of prior fracture, exposure to dialysis and use of glucocorticoids in maintenance immunosuppression regimens. The overall findings were similar in analyses that adjusted for fracture risk factors through multivariable analyses or the use of propensity score adjustment. Despite this, it is important to note that some fracture risk factors could not be ascertained. In particular, information was not available on alcohol use, smoking, weight bearing exercise, pre-transplant bone mineral density, severity of chronic kidney disease mineral and bone disorder, and use of preventive medications, such as vitamin D and bisphosphonates.[8] Other factors, such as prior fracture history and health status, could not be fully ascertained due to well described limitations of administrative data in which many chronic conditions are under-coded and coding practices may vary across providers and time[9]. Furthermore, functional impairment is assessed in the USRDS using standard data collection forms completed by providers. It is possible that mild to moderate degrees of impairment would be unknown to providers and therefore, not reported. Despite these limitations in ascertainment, the similar unadjusted prevalence of prior fracture reported in the pre-transplant period is reassuring.

So what may account for the reduction of fractures among patients with type 1 diabetes that received a simultaneous pancreas-kidney transplant? As suggested by the authors, restoration of endogenous insulin production and euglycemia may account for the observed benefit. This could be due to an attenuation of bone loss or a reduction in the rate of falls,

perhaps due to better control of diabetic complications and fewer episodes of insulin-induced hypoglycemia. An interesting finding in the study was that the difference in fracture rates was evident as early as 3 months post-transplant, suggesting a relatively acute effect. Furthermore, in contrast to many prior studies of fracture, this study includes both fragility fractures that occur in the setting of low-trauma, such as a fall from a standing height, and traumatic fractures that could be due to a higher rate of accidents and high-trauma falls, even in the absence of deficits in bone strength. Although these analyses are underpowered for individual fracture type, the strongest risk reduction due to simultaneous pancreas-kidney transplant versus kidney transplant alone was in pelvic fracture, a fracture subtype that can be related to bone fragility, but is also commonly seen in the setting of high-trauma injuries. This finding coupled with the early difference in fracture rates may suggest that the major mechanism of decreased fracture after simultaneous pancreas-kidney transplantation is due to better prevention of falls and injuries.

Interestingly, the authors found that the benefit of simultaneous pancreas-kidney transplant and fracture was present only in males. Although gender-based differences in the pathophysiology of fracture post-transplantation are possible,[10] other explanations need to be considered. The definition of fractures in this study was based on hospitalization billing codes, a methodology that may miss subclinical, non-hospitalized fracture events, such as vertebral compression fractures, that cause substantial morbidity, particularly in women.[10] Furthermore, detailed medication information was not available in the study. It is possible that due to the higher baseline rate of fragility fracture in women compared to men in the general population, women were more likely to receive medications aimed at fracture prevention, such as calcium, vitamin D, and anti-resorptive agents, or to undergo bone mineral density screening. More aggressive treatment and screening may have mitigated the benefits of simultaneous pancreas-kidney transplantation in women. Regardless of the proposed reasons, this gender difference should be interpreted cautiously in the setting of a non-statistically significant interaction coefficient. In addition, the number of fractures was not reported by sex, and it is possible that significance in one group is due to differences in statistical power in these subsets, as opposed to true biological differences. Confirmatory studies are needed to distinguish between these possibilities.

As noted by the authors, prior studies compared patients with type 1 diabetes after simultaneous pancreas-kidney transplant to all patients receiving kidney transplantation alone, including non-diabetics, and concluded that fracture risk was higher after simultaneous pancreas-kidney transplantation.[11] In the current study,[7] Nikkel *et al* demonstrate that the incidence of fracture among patients with type 1 diabetes receiving simultaneous pancreas-kidney transplant was intermediate between the lower risk among non-diabetic recipients of a kidney transplant alone and the higher risk among patients with type 1 diabetes receiving a kidney transplant alone. With this analysis, the authors reveal a likely explanation for the finding of higher risk after simultaneous pancreas-kidney transplant in prior reports that may have been due to confounding by type 1 diabetes. In this way, the current study provides critical new insights that will impact decision making for patients with type 1 diabetes pursuing kidney transplantation. The mechanisms that may account for this observed benefit cannot be definitively determined by this study design, but

could include reduction in bone loss or mitigation of fall risk due to better control of diabetic complications, or could be due to factors unrelated to effects on diabetes directly, such as differences in rejection episodes or imbalance in patient characteristics. Although the optimal study design to determine the impact of simultaneous pancreas-kidney versus kidney transplantation alone on fracture outcomes is a randomized controlled trial, randomization of a strongly preference-based decision, like transplantation, is not likely to be feasible. In this context, the current retrospective study provides valuable information and helps refine future hypotheses to study the mechanisms that underlie the apparent advantage of simultaneous pancreas-kidney transplant among men.

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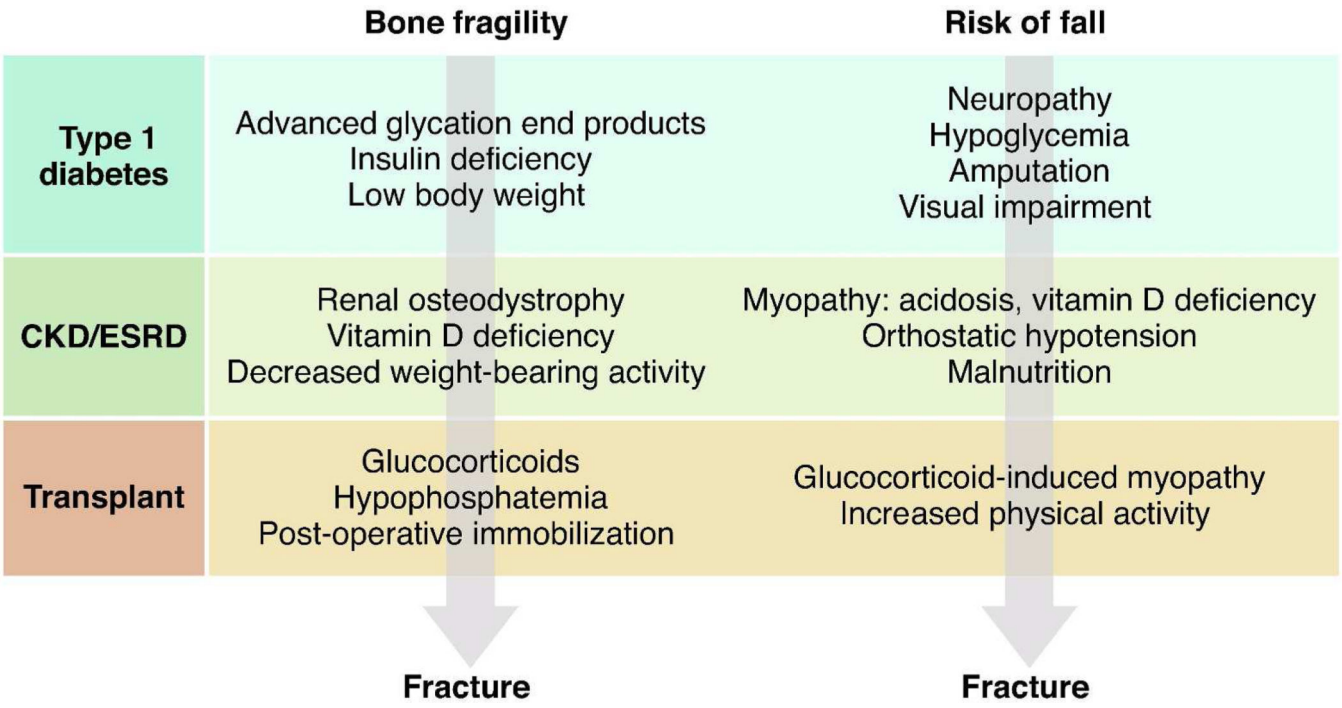

Figure.

Proposed mechanisms affecting risk of fracture in patients with type 1 diabetes after kidney transplantation. CKD, chronic kidney disease; ESRD, end-stage renal disease.