Fracture Risk in Kidney Transplant Recipients

Fractures after kidney transplantation are associated with morbidity (including acute and chronic pain)mortality, and high economic costs.

Fracture sites ranging from 3.3 to 99.6 fractures per 1000 person-years.

The 5-year cumulative incidence for fracture varied ranging from 0.85% to 27%.

Common factors associated with an increased fracture risk were

Older age

Female sex

The presence of diabetes

Receipt of dialysis before transplantation.

Other less common but statistically significant risk factors were

A previous history of fracture

Rreceipt of a kidney from a deceased (vs. living) donor.

Fracture Incidence and Fracture Location

Two studies included only fractures resulting in hospitalization

Two studies included only hip fractures one study included only foot fractures .

Hip fractures are founded an incidence rate of 3.3 fractures per 1000 person-years.

Conley et al. included multiple fracture sites and reported an incidence rate of 99.6 fractures per 1000 person-years.

Nikkel et al. found that recipients who received early corticosteroid withdrawal had an incidence rate of 5.8 fractures per 1000 person-years compared with 8.0 fractures per 1000 person-years in recipients who were given corticosteroid-based immunosuppression without early withdrawal.

For the six studies that considered multiple fracture sites, the most common site was the hip [three studies] and foot [two studies }

When multiple fracture locations were included, hip fractures accounted for 4.2% to 40% of fractures.

Fracture Incidence and Fracture Location

The 5-year cumulative incidence of fracture ranged from 0.85% to 27% (10, 14, 15, 17).

Kalker et al. (14) only included foot fractures in diabetic patients and found a 5-year cumulative incidence of 27%.

Opelz et al. (17) only included hip fractures and found a 5-year cumulative incidence of 0.85%.

Eight studies reported information on the timing of fracture after transplantation .

One study (6) found a linear increase in the cumulative hazard of fracture after transplantation,

one study (7) found that the fracture rate remained relatively constant over time,

one study (16) found that fracture incidence decreased at 1 and 2 years for kidney transplant recipients who had early corticosteroid withdrawal.

Ball et al. (12) found that, shortly after transplantation, the relative risk of fracture was more than 30% higher in recipients compared with dialysis patients.

However, 630 days after transplantation, patients still on dialysis and transplant recipients had an approximately equal risk of hip fracture (12).

Risk Factors for Fracture

- Age and Sex

Older age to be a significant risk factor for fracture (6, 15, 16).

Ages 45 to 65 years had a 14% higher risk of fracture compared with those ages less than 45 years (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.10–1.18). (15)

Female recipients had a higher risk of fracture compared with male recipients (6, 15, 16).

42% relative increase in the fracture rate among women compared with men (HR, 1.42; 95% CI, 1.31–1.55).(16)

Female recipients ages 60 years or more were at a statistically significant greater risk of fracture (HR, 5.1; 95% CI, 2.4–10.9).

Risk Factors for Fracture

Diabetes

- Diabetes was considered a potential risk factor in five studies (6, 13, 15–17) and was found to be significant in all but one study (17). Conley et al. (13) studied type 1 diabetics and found a HR of 2.0 (95% CI, 1.2–3.5).

Pretransplantation Dialysis

- Four of six studies reported that receipt of pre-transplantation dialysis significantly increased the risk of fracture (6, 12, 15, 16).

Specifically, Abbott et al. (6) found a 74% relative increase in fractures resulting in hospitalization for recipients who received dialysis before transplantation (odds ratio, 1.74; 95% CI, 1.02–2.96).

Risk Factors for Fracture

Prior Fracture

Fracture before transplantation was a risk factor for future fractures (6, 16).

A fracture before transplantation was associated with a higher risk of fracture after transplantation (HR, 2.82; 95% CI, 2.33–3.43).

Deceased Donor

- Two studies assessed the role of donor type (deceased vs. living) on fracture risk (15, 16).

Receipt of a kidney from a deceased (vs. living) donor significantly increased the risk of fracture. Specifically, Nikkel et al. (16) found that receiving a kidney from a deceased donor increased the risk of fracture by 36% (HR, 1.36; 95% CI, 1.24–1.49)

DISCUSSION

Despite being a topic of study since the 1970s, overall there remains poor consensus on the incidence and risk factors for fractures in kidney transplant recipients.

This information is important to transplant recipients and their physicians, because it guides

- prognostication
- clarifies fracture burden
- helps define sample size requirements for future prevention trials

DISCUSSION

Incidence rate of fractures varied widely from 3.3 to 99.6 fractures per 1000 person-years and was difficult to compare across studies. Similarly, the cumulative incidence was highly variable.

Rizzari et al. (10) found that the cumulative incidence for fracture at 5 years was only 5%. However, this was for nondiabetic patients, who were given a reduced prednisone regimen (nondiabetes status and reduced steroid dosage have some evidence of being protective against fracture) (15, 16).

The study with the lowest incidence rate of 3.3 fractures per 1000 person-years only included hip fractures.

Three of the four largest studies only included fractures that resulted in hospitalization (6, 12, 15, 16); this may introduce bias because fractures managed solely through the emergency room will not be recorded.

DISCUSSION

The study with the largest incidence, 99.6 fractures per 1000 person-years, included multiple fracture locations and did not limit fractures to those resulting in hospitalization (13).

Although a precise estimate of fracture is not known in kidney transplant recipients, it is likely to be substantially higher than the general population.

One study reported that female kidney transplant recipients ages 45 to 66 years had a fracture rate 34 times higher than the general U.S. population (7).

A higher risk of fracture in kidney transplant recipients compared with the general population may stem from:

underlying renal bone disease,

use of steroids and other

immunosuppressives,

increased risk of falls (19).

DISCUSSION

- The most common fracture locations from studies included in this review were hip fractures and ankle/foot fractures.
- Hip fractures together with vertebrae, humerus, and wrist fractures are considered to be the main sites for osteoporotic fractures (18).
- Hip fractures are particularly concerning given their high mortality and morbidity (20).
- In one study, where at the time of transplantation approximately 81% of the sample was ages 54 years or younger, the incidence rate was 3.3 hip fractures per 1000 person-years (12).
- In the general population, hip fractures in individuals ages 50 to 54 years has been found to be between 0.20 and 0.31 fractures per 1000 person-years

DISCUSSION

Older age

Female sex

Prior history of fracture

Presence of diabete

were all associated with an increased risk of fracture in kidney transplant recipients.

These factors are also well-known risk factors for fracture in the general population (18, 22).

In some primary studies, risk factors for fracture found to be unique to kidney transplant recipients included

Receipt of dialysis before transplantation

Receipt of a kidney from a deceased (vs. living) donor (6, 12, 15, 16).

However, as mentioned, overall there was poor consensus on transplant-specific risk factors for fracture.

This impairs our ability to identify those at highest risk for fracture who could be enrolled into prevention trials

Recommendations

- **First**, we recommend that studies assess fracture events rather than using a surrogate measure, such as bone mineral density (BMD).
- The utility of BMD as a predictor for fracture is unclear, because many individuals with low BMD will not fracture (30, 31).

  But Akaberi et al. (32) found that low BMD was a strong, independent predictor of fracture.

- **Second,** fractures should be presented both as composite of fracture locations and by fracture location and ascertained according to accepted definitions.

- An understanding of the incidence of fractures is needed to guide sample size calculations in future clinical trials to ensure that they have adequate statistical power.
- Palmer et al. (33) and Stein et al. (34) conducted meta-analyses on fracture prevention therapies in transplant recipients and found that the studies were inadequately powered to determine whether the therapies were effective at reducing fracture events.
- In other words, there is currently insufficient information on which treatments can decrease fracture risk in recipients (33, 35).
- **Third,** we need larger and longer studies that identify risk factors for fracture—this will allow us to develop tools to identify those at high fracture risk.

Recommendations

- **Fourth,** Given that older age is a risk factor for fracture, an increase in the average age of recipients may lead to an increase in the number of fractures (18)

Transplants that took place after 2000

- Only 4 of the 10 prior studies included transplants that took place after 2000, when induction regimens were changed (i.e., trend toward a prednisone-free regimen) (37).
- The impact that steroid-sparing regimens will have on fracture rates remains controversial. Although one study on kidney transplant recipients suggested that steroid-sparing regimens decreased fracture incidence, another study found a similar fracture incidence to those who did not receive a steroid-sparing regimen (16, 38). Prospective studies are needed on this topic (39).
- Finally, we need to know which periods after transplantation have the greatest risk of fracture, because this is currently unknown.

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Interventions for Preventing Bone Disease Following Kidney Transplantation: Is There Evidence for Specific Therapy?

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- In (CKD), disorders of mineral metabolism are a major cause of morbidity. As the prevalence of kidney disease and rate of kidney transplantation both increase, there is a growing prevalence of CKD-MBD among transplant recipients.
- **Before** kidney transplantation, CKD-MBD affects almost all patients with CKD.
- **Posttransplantation**, many patients still have some degree of reduced kidney function, as well as transplant-associated disturbances in mineral metabolism.
- **The prevalence** of osteoporosis in the posttransplantation population is ~30%, and a 2009 report estimated the fracture rate of transplant recipients to be approximately 4 times that of the general population, with an estimated 22.5% of patients experiencing a fracture within the first 5 years following transplantation.

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- A review of 4,821 TX recipients found an overall 5- and 10-year cumulative incidence of nonvertebral fractures of 2.7% (95% confidence interval [CI], 2.2%-3.2%) and 5.5% (95% CI, 4.6%-6.5%), respectively.
- This declining rates might be related to significant decreases in the use of prednisone and cyclosporine.
- The clinical ramifications of a fracture in the transplantation population remain profound.
- There is 60% increased risk for death associated with a hip fracture in the post–kidney transplantation population versus the general population.

Pharmacologic Therapies for Posttransplantation CKD-MBD

potential pharmacologic strategies that could be used to treat and prevent bone disease in kidney transplant recipients

Nutritional Vitamin D

-Cholecalciferol

-Ergocalciferol

Vitamin D Receptor Activators (VDRAs)

-Calcitriol

-Paricalcitol

-Doxercalciferol

Calcimimetics

-Cinacalcet

Anabolic Agents

-Teriparatide

Anti-Resorptive Agents

-Bisphosphonates

-Calcitonin

-Denosumab

potential pharmacologic strategies that could be used to treat and prevent bone disease in kidney transplant recipients

- However, due to limited available evidence management of bone disease posttransplantation generally matches strategies used in managing patients with CKD-MBD.
- In 2017, KDIGO published a guideline with a special section on the management of CKD-MBD in transplant recipients.[5]
- On account of biochemical changes in a newly functioning graft, the guideline recommends measuring serum calcium and phosphate concentrations weekly after transplantation.
- After values stabilize, measurement frequency should be based on clinical judgment.

potential pharmacologic strategies that could be used to treat and prevent bone disease in kidney transplant recipients

- KDIGO suggests that measuring vitamin D concentrations and correction of deficiency should parallel that done in the general population.

- One key means to prevent and limit the effects of MBD posttransplantation is to minimize glucocorticoid use

potential pharmacologic strategies that could be used to treat and prevent bone disease in kidney transplant recipients

- A previous Cochrane Review published in 2007 failed to demonstrate that any therapy reduced fracture risk compared to placebo.
- The evaluated therapies included vitamin D, bisphosphonates, and calcitonin.
- Palmer et al, have recently updated the Cochrane Review of interventions for preventing and treating bone disease in kidney transplant recipients.
- In contrast to the initial report, which evaluated 24 trials (1,299 participants), this analysis included 45 studies (2,698 participants) with a median follow-up of 12 months.
- In addition, this analysis also included studies evaluating calcimimetics (cinacalcet), RANKL inhibitors (denosumab), and synthetic human parathyroid hormone (teriparatide), as well as parathyroidectomy.

Bisphosphonates

bisphosphonates may prevent fractures following kidney transplantation, although the 95% CI included the possibility that bisphosphonate therapy might make little or no difference in fractures.

These data are limited in that most participants received

bisphosphonates within 1 month of transplantation independent of bone mineral density measurements and were treated for 1 year.

There tended to be some hypocalcemia with bisphosphonates and there was no effect on vascular calcifications or mortality.

There was no measurable effect of vitamin D compounds on fractures or vascular calcifications.

The only study evaluating parathyroidectomy was a comparison with cinacalcet, and in this study there was only 1 fracture and the investigators reported no differences in vascular calcification scores.

Unfortunately, this updated Cochrane Review does not provide substantive new information from the original and suggests that bisphosphonate therapy after kidney transplantation may make little or no difference to fracture rates.

- Although there are several studies with other therapies, none of them were designed adequately to evaluate their impact on CKD-MBD.
- Although prevention of fractures is an important end point, CKD-MBD is a complex pathophysiologic process that should be appropriately identified and treated in transplant recipients, similar to the approach used with patients with CKD before transplantation.
- Thus, the persistent disturbances of mineral metabolism, involving calcium, phosphate, parathyroid hormone, vitamin D, fibroblast growth factor 23, and sclerostin, in addition to effects of immunosuppression medications, graft function, and dysfunction need to be addressed following transplantation.

- Finally, assessment of bone turnover may be important in deciding on specific therapy.
- In studies of transplant recipients who have undergone bone biopsies, low-turnover (adynamic) bone disease is seen in up to 50%, and high-turnover disease due to persistent hyperparathyroidism is seen in 25% to 50%.
- Thus, the use of bisphosphonates, the agent predominantly evaluated in the Cochrane Reviews, could be problematic.
- Although bisphosphonates may attenuate bone loss after transplantation, they could increase the risk for low-turnover bone disease which may actually increase fractures and vascular calcifications.

- Treatment of persistent or worsening hyperparathyroidism, which is a risk for both fractures and vascular calcifications, was not addressed by this analysis, except for the few studies that evaluated the use of calcimimetics and parathyroidectomy.
- Of interest, the use of bisphosphonates, which may cause hypocalcemia, could worsen hyperparathyroidism.
- In patients with persistent hyperparathyroidism and hypercalcemia refractory to medical management, surgical parathyroidectomy should be an appropriate treatment option.
- Although there are no data on the effects of parathyroidectomy on reducing fractures in patients with tertiary hyperparathyroidism, parathyroidectomy (subtotal or total) was shown to be more effective at curing tertiary hyperparathyroidism compared with those who underwent medical management

- CKD-MBD is a complex pathophysiologic process of which fractures are only one of the potential negative outcomes.
- Refractory hyperparathyroidism
- vascular and soft tissue calcifications
- progressive cardiovascular disease
    - All are also the result of poorly controlled CKD-MBD.
- Unfortunately, most studies and the resultant Cochrane Reviews predominantly addressed fractures and “osteoporosis,” using predominantly anti-osteoporosis therapies, but need to evaluate all the components of CKD-MBD

- Future studies have to address each component and then evaluate the appropriate clinical end point, which would include:
- fractures
- cardiovascular disease
- progressive hyperparathyroidism
- bone mineral abnormalities

long-term studies need to be designed to address both the potential beneficial and detrimental effects of these therapies.