DERLEME REVIEW

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Falls in Kidney Transplant Recipients: Traditional Review

Böbrek Nakli Alıcılarında Düşme: Geleneksel Derleme

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ABSTRACT Kidney transplantation is the gold standard treatment for end stage renal disease. Despite the improvement in survival and quality of life, the prevalence of falls is higher in kidney transplant recipients. Factors that increase the risk for falls include female gender, older age, impaired balance control, lower ankle dorsiflexion muscle strength, high serum creatinine levels, and the use of antidiabetic medications. Functional limitations, fatigue, low cardio-respiratory fitness, changes in mineral metabolism lead to bone mineral disease in chronic kidney disease and can finally play an important role in occurrence of accidental falls in pre-transplantation period. Fractures without dislocations or head injury-related hemorrhages constitute a majority for the serious fall-related injury types. In addition to many factors such as cumulative dose of corticosteroids, younger age at transplantation, hyperparathyroidism, vitamin D deficiency and renal osteodystrophy, risk of falls also contribute to increased post-transplantation bone loss and fracture risk. Hip fractures requiring hospitalization in the post-kidney transplant period are associated with a higher risk of mortality. It is important to understand the underlying mechanisms for falls in kidney transplant recipients in order to prevent severe injuries including fractures and decrease healthcare costs. The awareness of healthcare professionals should be increased for falls in this specific population to design multidisciplinary therapeutic approaches including risk factor assessment, exercise programs and patient and caregiver education not only for kidney transplant recipients but also for the patients waiting on a transplantation list.

Keywords: Balance control; falls; kidney transplantation

ÖZET Böbrek nakli, son dönem böbrek yetersizliğinin tedavisinde altın standarttır. Yaşam kalitesi ve sağkalımdaki gelişmelere rağmen böbrek nakli alıcılarında düşme prevalansı yüksektir. Kadın cinsiyet, ileri yaş, bozulmuş denge kontrolü, azalmış ayak bileği dorsifleksör kas kuvveti, yüksek serum kreatinin düzeyi ve antidiyabetik ilaç kullanımı düşme riskini artıran faktörler arasında yer almaktadır. Fonksiyonel limitasyon, yorgunluk, düşük kardiyo-respiratuar uygunluk, mineral metabolizmasındaki değişiklikler kronik böbrek yetersizliğinde kemik mineral hastalığına yol açmaktadır ve sonuçta nakil öncesi dönemde kazara düşmelerin oluşmasında önemli bir rol oynamaktadır. Dislokasyon olmaksızın görülen kırıklar veya kafa travmasına bağlı görülen hemorajiler düşmeyle ilişkili ciddi yaralanmaların büyük bir kısmını oluşturmaktadır. Kümülatif kortikosteroid dozu, erken yaşta nakil olmak, hiperparatiroidizm, D vitamini eksikliği ve renal osteodistrofi gibi birçok faktöre ek olarak düşme riski de böbrek nakli sonrası kemik kaybı ve kırık riskinin artmasına neden olmaktadır. Böbrek nakli sonrası dönemde, hastane yatışı gerektiren kalça kırıkları yüksek mortalite riskiyle ilişkilidir. Böbrek nakli alıcılarında kırıkları içeren ciddi yaralanmaları önlemek ve sağlık harcamalarını azaltmak için düşmeyle ilişkili mekanizmaların anlaşılması önemlidir. Böbrek nakli alıcılarında ve böbrek nakli öncesi nakil listesinde bekleyen hastalarda risk faktörlerinin değerlendirilmesi, hasta ve hastaya bakım verenlerin eğitimi ve egzersiz programını içeren multidisipliner terapötik yaklaşımlar tasarlamak için sağlık profesyonellerinin bu özel popülasyondaki düşmelere yönelik farkındalığı artırılmalıdır.

Anahtar Kelimeler: Denge kontrolü; düşme; böbrek nakli

Kidney transplantation is the best treatment option for end stage renal disease and is associated with remarkable benefits of survival and quality of life.[1] Even if kidney function improves after transplantation, kidney transplant recipients (KTR) have still chronic kidney disease in addition to gradual decrease in graft function due to chronic allograft nephropathy.[2] Because of risk factors including chronic kidney disease, glucocorticoid-induced osteoporosis and aging, KTRs could have high-risk for sarcopenia.[2] The prevalence of sarcopenia in KTRs ranging from 11.8 to 49.6% is associated with impaired renal function.[2,3] Bone diseases, changes in bone density and bone quality are one of the major causes of post-kid-

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ney transplant morbidity.[4] Rapid bone loss occurs especially during the first six months after transplantation. Glucocorticoids, usually prescribed in high doses after transplantation, have reported to be responsible for low femoral neck and lumbar spine bone mineral density.[5] KTRs have high fracture risk compared to general population and patients receiving dialysis.[6,7] Functional limitations, fatigue, low cardio-respiratory fitness, changes in mineral metabolism lead to bone mineral disease in chronic kidney disease and can finally play an important role in occurrence of accidental falls in pre-transplantation period.[8] In addition to many factors such as cumulative dose of corticosteroids, younger age at transplantation, hyperparathyroidism, vitamin D deficiency and renal osteodystrophy, risk of falls also contribute to increased post-transplantation bone loss and fracture risk.[4]

In fact, falls risk is not only a post-transplant consequence, but also higher in patients on transplantation waiting list. Therefore, understanding of the underlying mechanisms for fall risk in patients with chronic kidney disease, will help to prevent falls in post-transplant period.

There are many studies addressing falls and the consequences of falls in KTRs, but none of them are review articles. In this context, the literature was searched using the keywords such as kidney, renal, kidney transplant, chronic kidney disease, end-stage kidney disease, falls, risk factors for falls, fracture, consequences of falls. So, we synthesized the current kidney transplant literature to provide information healthcare professionals in this review.

FALLS RISK IN PATIENTS WAITING FOR KIDNEY TRANSPLANTATION

Adult patients of all ages with end-stage kidney disease have a higher risk for falls, similar to community-dwelling older adults, and falls occur in 1.2-1.7 per patients-year among patients undergoing hemodialysis and peritoneal dialysis.[9] In chronic kidney disease, falls are a result of complex interaction of risk factors including female gender, older age, psychotropic medication and polypharmacy (specifically responsible for postural hypotension), cognitive dysfunction, comorbidities, malnutrition, hemodynamic and metabolic instability caused by dialysis therapy, muscle weakness, frailty, and impaired balance control.[10,11]

Uremic syndrome occurs parallel to a gradual decline in glomerular filtration rate and, as a compensation mechanism, multiple sclerosis develops in the endothelial layer leading to decreased nephron function and accumulation of toxins and wastes. Hence, uremic myopathy occurs due to the toxic effects on muscle cell mitochondria.[12] Hellberg et al. indicated relationships between decreased glomerular filtration rate, an important parameter for kidney function, and lower physical performance and also frailty.[13] In kidney transplant candidates, a history of falls and recurrent falls are associated with lower extremity impairment and frailty. The most important points for the falls in kidney transplant candidates are the decreased chance of listing and increased risk of transplant waitlist mortality.[14] Therefore, fall risk should be addressed in detail for this population and preventive approaches should be planned for each risk factor during the whole transplantation waiting process.

FALLS IN KTRS

Kidney transplantation provides better outcomes than dialysis, however at least a period of dialysis history is a risk factor for serious fall injuries in patients with end stage renal disease. Fall injuries could adversely affect access to kidney transplantation even on a waiting list. End-stage renal disease patients with a history of serious fall injuries have less likely to be waitlisting and have lower chance of receiving a kidney transplant.[15] Lynch et al. indicated a 2.8% prevalence of serious fall injuries in KTRs, and longer length of stay, increased graft failure and lower postoperative survival which were associated with serious fall injuries during the last pre-transplant year.[16] Fractures without dislocations or head injury-related hemorrhages constitute a majority for the serious fall-related injury types.[16] Remarkably, hip fractures required hospitalization were associated with higher mortality risk after kidney transplantation.[17] Therefore, it is very important to clarify the underlying mechanisms and prevent falls in KTRs to improve

graft survival, diminish fracture risk and healthcare costs.

A fall is defined as 'an event which results in a person coming to rest inadvertently on the ground or floor or other lower level' by The World Health Organization.[18] Balance control is required to achieve many static and dynamic activities in daily life and impaired balance control can lead to falls. Therefore, assessment of balance control using either objective methods or clinical tools could help to detect increased fall risk. Zanotto et al. showed a deterioration in balance control of KTRs compared to healthy controls.[19] In another study, Zanotto et al. evaluated balance control using stabilometric platform and indicated 1.6-4.3 times greater fall prevalence in KTRs than general population.[20] They also reported poor balance control as a significant risk factor for falls after kidney transplantation.[20] In addition to these objective measurements, functional clinical tools for fall risk can also be used. Lorenz et al. compared balance control using Short Physical Performance Battery before and after transplantation.[21] Deteriorated balance control performance in pre-transplant period was associated with higher risk of longer hospitalization and 30-day rehospitalizations following transplantation.[21] Esposito et al. assessed KTRs with Timed Up & Go Test (TUG) and reported significant mobility limitations, indicated as TUG duration more than 10 seconds, in 21.9% of the patients.[22] TUG scores were inversely associated with glomerular filtration rate and muscle strength. 3.8% of the patients in that study have fallen at least once in the last year.[22] Sedaghat et al. showed an association between lower glomerular filtration rate and higher prevalence of fall in participants with poor gait performance.[23] Impaired kidney function could impact gait performance via the accumulation of neurotoxins leading to b2-microglobulin deposition in joints and connective tissue, axonal demyelination and augmented inflammatory cytokines, consequently these factors might cause loss of muscle mass, muscle weakness and poor balance control.[23] Balance impairments and mobility limitations in KTRs may inversely affect functional independence in daily life activities.

RISK FACTORS FOR FALLS IN KTRS

FEMALE GENDER AND OLDER AGE

Individual's gender and age may influence unintentional falls.[24] Due to the prolonged life expectancy, the incidence of increases in women parallel to aging.[24] Female gender and increased age (≥65 years) have been found to be the determinants of fall risk in hemodialysis patients suggesting the importance of bone structure changes as a consequence of decreased estrogen levels.[25] In a study of Naylor et al., 3-year cumulative incidence of falls was 7.9% in overall participants, but the highest incidence was in women KTRs aged 50 years or older (11.1%).[6] The factors mentioned above may be responsible for increased fall rates in female recipients, but further research are required to measure the possible effects of gender and older age on fall risk after kidney transplantation.

BALANCE CONTROL

Poor balance control has been identified as one of the main risk factors for falls in elderly people.[26] Kasbia et al. found impairments in balance control by using TUG in most of elderly KTRs and 21% of their participants experienced an accidental fall at least once in the last 12 months.[27] Even though, Zanotto et al.'s study population was remarkably younger (mean age=52.3 years), 33.9% of their participants had a history of fall at least once in the last year.[20] In their study, balance control performance was worse for fallers and poor balance control was found to be a significant risk factor for falls in KTRs.[20] Malnutrition, oxidative stress, and chronic inflammation leading to muscle weakness in chronic kidney disease, may result in poorer balance performance.[20] The other mechanism for impaired balance control may include neurotoxic side effects of immunosuppressive treatment such as peripheral neuropathy and tremor.[20] Although Lorenz et al. showed improvements in balance performance following kidney transplantation, Zanotto et al. indicated a worse balance control in KTRs compared to healthy controls suggesting a poorer capacity of relying on proprioceptive information.[19,21]

MUSCLE STRENGTH

Loss of peripheral and respiratory muscle strength is one of the most common complications in KTRs. Painter et al. found lower muscle strength and mass in a kidney recipient compared to his twin donor.[28] Although the muscle fiber composition was identical, the cross sectional area of all muscle fiber types were decreased in twin recipient.[28] Alterations in protein synthesis as a consequence of kidney failure may have effect the muscle ultrastructure.[28] In Harada et al.'s study, successful kidney transplantation resulted in reductions in water, bone and muscle mass, while increasing body fat mass without changing the body mass index.[29] Increased fat mass could inversely affect muscle mass, presumably chronic inflammatory situation caused by high body fat, which also contributes to a decrease in muscle mass and strength.[30]

Sarcopenia is defined as the age-related involuntary loss of skeletal muscle mass, strength, and function.[31] Yanishi et al. demonstrated the relationship between longer duration of dialysis and increased incidence of sarcopenia, suggesting the relationship between protein intake restriction during dialysis period and post-transplant sarcopenia.[30] Floriano et al. also showed a positive correlation between uric acid levels and muscle mass/strength of the lower limb muscles in KTRs suggesting the possible protective properties of uric acid against the excesses of reactive oxygen and nitrogen species influencing muscle fiber activation, size and excitation-contraction.[32] Another predisposing factor for decreased muscle mass is new-onset diabetes after kidney transplantation. Adachi et al. observed increases in intramuscular adipose tissue content aggravated by the new-onset diabetes in KTRs.[33] It may be attributed to the higher blood levels of interleukin-6 and C-reactive protein resulting in insulin resistance and reduce in muscle mass particularly in sarcopenic obesity.[33] Insulin has a role to stimulate protein synthesis and lower extremity neuropathy has been found to be strongly associated with muscle weakness in diabetic patients due to decreased muscle synthesis.[33]

Significant increases in respiratory and peripheral muscle strength were found following kidney transplantation compared to pre-transplant period.[34] However, respiratory muscle strength were still below normal levels and peripheral muscle strength was significantly lower than healthy controls.[34,35] Zanotto et al. showed ankle dorsiflexion muscle strength was considerably lower for fallers and was a predictor factor of fall risk in KTRs.[20] Kestenbaum et al. found a direct association between impaired skeletal muscle mitochondrial bioenergetics and poor physical performance measured by 6-minute.[36] Although the underlying mechanism is not clearly defined, dysfunction of mitochondrial metabolism may impair functional independence.

INCREASED SERUM CREATININE

The monitoring of kidney functions in the first year after transplantation is important for renal graft function and survival.[37] Serum creatinine is the most widely used biomarker of kidney function. Creatinine can also be used in acute rejection episodes and in combination with blood drug concentrations to assess the toxicity of immunosuppressants.[37,38] In study of Odden et al., increased serum creatinine levels were associated with higher rates of functional limitation after adjustment for age, chronic health conditions, lean mass, physical activity and physical function in the elderly.[39] Although the direct relation between serum creatinine level and fall risk in KTRs has not been studied yet, fall incidence was reported to be higher in KTRs with increased serum creatinine levels compared to patients with normal serum creatinine level.[40]

ANTIDIABETIC MEDICATIONS

Diabetes mellitus is the most common cause for chronic kidney disease.[41] New-onset diabetes is also one of the most common complications after kidney transplantation affected by age, ethnicity, obesity, immunosuppression, and cytomegalovirus infection.[42] New-onset diabetes is associated with increased morbidity, cardiovascular disease, graft failure and the health-care costs.[42] Insulin or oral hypoglycemic medications are commonly used for hyperglycemia. However, studies indicated the effect of insulin therapy on increased fall risk compared to oral antidiabetic agents.[43] Inversely, oral medications such as metformin and thiazolidinedione, have not been shown to have a direct relationship with fall incidence

although metformin was reported to be associated with vitamin B_{12} deficiency which could increase fall risk causing peripheral neuropathy.[44] Thiazolidinedione have been demonstrated to increase the risk of fractures.[43] There is insufficient evidence in different populations, although in study of Tekkarismaz et al., fall incidence increased in KTRs parallel to the use of oral antidiabetic medications.[40] Various antidiabetic medications are used to overcome new-onset diabetes after kidney transplantation. Although the underlying mechanism is not clearly defined, the possible effects of antidiabetic drugs on falls should be addressed in further studies.

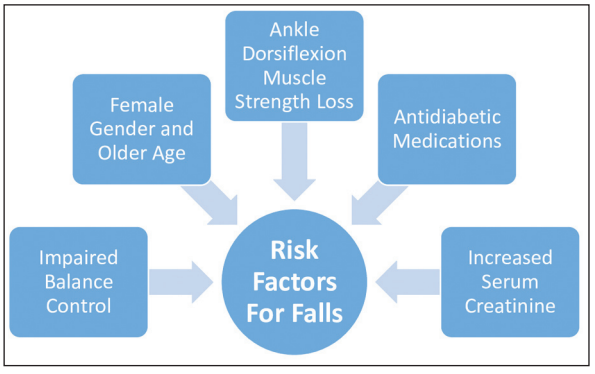

FIGURE 1: Possible risk factors for falls after kidney transplantation.

CONCLUSION

Falls are multifactorial after kidney transplantation (Figure 1). Female gender, older age, impaired balance control, lower ankle dorsiflexion muscle strength, increased serum creatinine levels and antidiabetic medications are predisposing factors associated with increased risk of falls. Falls and fall related injuries lead to graft failure and increased healthcare costs. Therefore, awareness of clinicians and health care providers for falls and risk factors need to be increased and severe consequences associated with falls increasing morbidity and mortality should be prevented by a multidisciplinary approach. KTRs should be screened for fall related risk factors, and prevention of falls are very important to improve patient outcomes after kidney transplantation. Effective strategies should be planned including fall recording procedures, long term follow-up screenings, multidimensional risk factor analysis, exercise programs, therapeutic interventions, and patient and caregiver education not only for KTRs but also for the patients waiting on a transplantation list.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hatice Nihan Bozkurt, Meriç Yıldırım;* ***Control/Supervision:*** *Meriç Yıldırım;* ***Literature Review:*** *Hatice Nihan Bozkurt, Meriç Yıldırım;* ***Writing the Article:*** *Hatice Nihan Bozkurt;* ***Critical Review:*** *Meriç Yıldırım.*

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