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Avascular Necrosis and Risk Factors in Kidney Transplant Recipients: A Single-Center Experience

Böbrek Nakli Alıcılarında Avasküler Nekroz ve Risk Faktörleri: Tek Merkez Deneyimi

Ömer Faruk Akçay, Asil Demirezen, Veysel Baran Tomar, Ozant Helvacı, Galip Güz

Gazi University Faculty of Medicine, Department of Nephrology, Ankara, Türkiye

Abstract

Objectives: Renal osteodystrophy, osteoporosis, bone fractures, and avascular necrosis (AVN) are prevalent complications observed in the post-transplant period among kidney transplant recipients (KTRs). Despite notable advancements, AVN remains a significant and devastating complication following kidney transplantation (KT).

Materials and Methods: The study included all patients who underwent KT at our transplantation unit and had at least one year of routine follow-up (n=343). Cases of symptomatic AVN were diagnosed by X-radiation, radioisotope bone scan, or magnetic resonance imaging. We evaluated the baseline characteristics, laboratories, and immunosuppressive treatments of KTRs.

Results: The frequency of AVN in our KTRs was 7.9% during the follow-up period, with a median diagnosis time of 15.2 (10.2-34.9) months. In KTRs with AVN, the leading cause of end-stage renal disease was glomerulonephritis (GN) (52% vs. 20%, p<0.001), and more rejection episodes occurred at follow-up (33% vs. 15%, p=0.01). In univariate analysis, GN [odds ratio (OR): 4.325, 95% confidence interval (CI), 1.936-9.661], cumulative steroid dosage at the post-transplant first year (OR: 1.001, 95% CI, 1.000-1.002), and rejection episodes (OR: 2.792, 95% CI, 1.185-6.578) detected as possible risk factors for AVN. Upon multivariate analysis, GN was identified as an independent risk factor for the development of AVN (OR: 4.373, 95% CI, 1.935-9.880, p<0.001).

Conclusion: Our study found GN to be associated with an increased risk of AVN. A higher prevalence of AVN may attributed to long-term pre-transplant steroid therapy in this group. In KTRs with a history of GN, greater awareness should be paid to cumulative steroid dosages, and early discontinuation of steroids may be considered.

Keywords: Avascular necrosis, glomerulonephritis, mineral bone disease, renal transplantation, steroid therapy

Öz

Amaç: Renal osteodistrofi, osteoporoz, kemik kırıkları ve avasküler nekroz (AVN), böbrek nakli alıcılarında (BNA) transplantasyon sonrası dönemde yaygın komplikasyonlardır. Kaydedilen önemli ilerlemelere rağmen, AVN böbrek nakli (BN) sonrası hala ciddi ve yıkıcı bir komplikasyon olmaya devam etmektedir.

Gereç ve Yöntem: Çalışmaya, transplantasyon ünitemizde BN yapılan ve en az bir yıl düzenli takip edilen tüm hastalar (n=343) dahil edildi. Semptomatik AVN vakaları röntgen, radyoizotop kemik taraması veya manyetik rezonans görüntüleme ile teşhis edildi. BNA'ların temel özellikleri, laboratuvar sonuçları ve immünsüpresif tedavileri değerlendirildi.

Bulgular: BNA'larda AVN sıklığı %7,9 olup, medyan teşhis süresi 15,2 (10,2-34,9) ay olarak belirlendi. AVN gelişen BNA'larda, son dönem böbrek hastalığının en yaygın nedeni glomerulonefrit (GN) idi (%52'ye karşı %20, p<0,001) ve takip sürecinde daha fazla rejeksiyon epizodu görüldü (%33'e karşı %15, p=0,01). Tek değişkenli analizde GN [olasılık oranı (OR): 4,325; %95 güven aralığı (GA), 1,936-9,661], nakil sonrası ilk yıldaki kümülatif steroid dozu (OR: 1,001; %95 GA, 1,000-1,002) ve rejeksiyon epizodları (OR: 2,792; %95 GA, 1,185-6,578) AVN için olası risk faktörleri olarak saptandı. Çok değişkenli analizde ise GN, AVN gelişimi için bağımsız bir risk faktörü olarak belirlendi (OR: 4,373; %95 GA, 1,935-9,880; p<0,001).

Address for Correspondence/Yazışma Adresi: Ömer Faruk Akçay
Gazi University Faculty of Medicine, Department of Nephrology, Ankara, Türkiye
E-mail: xxxxxxx **ORCID ID:** orcid.org/0000-0001-6587-4938

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Sonuç: Çalışmamız GN'nin AVN riskini artırdığını göstermiştir. Bu grupta AVN'nin daha yüksek prevalansı, uzun süreli nakil öncesi steroid tedavisine bağlanabilir. GN öyküsü olan BNA'larda kümülatif steroid dozlarına daha fazla dikkat edilmesi ve steroidlerin erken kesilmesi düşünülebilir.

Anahtar Kelimeler: Avasküler nekroz, glomerülonefrit, mineral kemik hastalığı, böbrek nakli, steroid tedavisi

Introduction

Kidney transplantation (KT) is considered the gold standard for managing kidney failure, offering recipients significant long-term advantages, such as enhanced survival rates and an improved quality of life (1). However, bone disease is commonly observed among kidney transplant recipients (KTRs), including conditions such as renal osteoporosis, bone fractures, and avascular necrosis (AVN). These bone diseases result from the ongoing effects of chronic kidney disease-mineral and bone disorder (CKD-MBD), as well as the influence of immunosuppressive therapies on bone health following transplantation (2). Although KT significantly improves patient outcomes, it does not entirely reverse the underlying CKD-MBD (3).

AVN is a debilitating bone condition that can arise in KTRs in the setting of CKD-MBD, frequently resulting in significant functional impairment. Prior to the development of modern immunosuppressive therapies, and mainly due to the effects of high-dose glucocorticoid treatments used in earlier years, AVN affected around 40% of KTRs (4). However, with recent advancements in both transplantation techniques and immunosuppressive strategies, the incidence of AVN has dropped to less than 5% (5,6). Despite these significant improvements, AVN remains a serious complication that continues to affect the quality of life of KTRs, emphasizing the importance of ongoing research and improved management approaches.

The underlying pathophysiological process of AVN is a compromised blood flow to the bone, which triggers necrosis and leads to progressive bone damage (7). Steroid-induced suppression of bone formation plays a significant role in bone loss, as glucocorticoids enhance osteoclast activity while exerting toxic effects on osteoblasts (8). The femoral head is most often the site of involvement, with other weight-bearing long bones also commonly affected. Some potential risk factors identified for AVN including diabetes, secondary hyperparathyroidism (HPT), and autoimmune diseases (9-11). Effective treatment focuses on preventing the collapse of these compromised bones, making it crucial to identify high-risk patients and detect AVN in its early stages.

To address this issue, we conducted a retrospective analysis to determine the prevalence of AVN, paying particular attention to the impact of patient demographics and post-transplant factors on its development. We aimed to identify the key risk factors for AVN and evaluate its clinical outcomes in KTRs under modern immunosuppressive therapy.

Materials and Methods

Study Population and Data Collection

The study included all patients who underwent KT in our transplantation unit and maintained regular follow-up. However, individuals under 18 years of age at the time of KT or with a follow-up duration of less than one-year post-transplantation were excluded. Clinical and demographic data were gathered, encompassing age, gender, smoking status, renin-angiotensin-aldosteron system (RAAS) inhibitors treatment, primary causes of end-stage renal disease (ESRD), and comorbid conditions like diabetes mellitus and hypertension. Additionally, we assessed transplantation-specific factors, such as type of donor (living or deceased), induction therapy, delayed graft function (requiring dialysis within the first week post-transplant), immunosuppressive treatment, the development of new-onset diabetes after transplantation, biopsy-confirmed rejection episodes, and cases of allograft failure. Laboratory evaluations encompassed estimated glomerular filtration rate, serum parathyroid hormone (PTH) levels, and proteinuria measurements. We utilized laboratory values obtained three months after KT as the baseline. This approach was taken to minimize the influence of early fluctuations in renal function and to ensure its stabilization. Persistent HPT was defined as PTH levels exceeding the upper reference threshold of our laboratory (>88 pg/mL) within the first year after transplantation.

Symptomatic AVN was identified using standard anterior-posterior pelvic X-radiation, radioisotope bone scans, or magnetic resonance imaging of the shoulder, knee, hip, or pelvis. In addition, various medical and surgical interventions for AVN have been documented, including steroid withdrawal, hyperbaric oxygen therapy, core decompression, and joint replacement. Gazi University Ethics Committee approved the study protocol (protocol number: E-77082166-604.01-1148721, date: 21.01.2025) under the Declaration of Helsinki and ethical standards for human research. Since this was a retrospective study and all procedures were part of standard clinical care, informed consent was not required.

Immunosuppression and Rejection Treatments

The choice of induction therapy (none, basiliximab, or antithymocyte globulin) was determined based on the immunological risk profile of the recipients. All patients received 500 mg of intravenous methylprednisolone (MPZ) on

the day of surgery. The initial dose was reduced by half over the subsequent days and then switched to a daily oral regimen of 20 mg prednisolone. The dosage was progressively decreased by 5 mg every two weeks until a maintenance level of 5-10 mg was achieved. In the absence of contraindications, a minimum daily dose of 5 mg prednisolone was continued during routine follow-up. The maintenance immunosuppressive regimen included prednisolone in combination with a calcineurin inhibitor (CNI), such as tacrolimus or cyclosporine, along with an antimetabolite, either mycophenolate mofetil or azathioprine. Mammalian target of rapamycin inhibitors was considered an alternative treatment option for patients who could not tolerate the side effects of CNI or antimetabolite treatment.

Suspected cases of acute rejection were evaluated through kidney biopsy and classified according to the Banff criteria (12). Treatment involved an initial course of intravenous steroids at doses ranging from 250 to 500 mg for 3 to 5 days, followed by oral steroids at a daily dose of 1 mg/kg. For patients on cyclosporine, tacrolimus was initiated. The cumulative oral and bolus corticosteroids administered during the first year post-transplantation were also calculated.

Statistical Analysis

Numerical data were summarized using descriptive statistics based on their distribution. Variables with a normal distribution were presented as means with standard deviations, while those without a normal distribution were expressed as medians with interquartile ranges. Nominal data were represented by counts (n) and percentages (%). The Mann-Whitney U test was used for group comparisons of variables that did not follow a normal distribution, while the independent samples t-test was applied to variables with a normal distribution. Nominal variables were compared using chi-square or Fisher's exact tests. Binary logistic regression analyses were conducted to identify independent risk factors linked to AVN. Variables with a p-value below 0.1 in the univariate analysis were included in the multivariate analysis. Statistical significance was defined as a p-value of less than 0.05. All statistical analyses were performed using SPSS software, version 20.0 (IBM Corp., Chicago, IL, USA).

Results

The study included 343 KTRs, with a mean follow-up duration of 125.3±68.9 months. Among the cohort, 37% (n=127) were female, and the average age at the time of transplantation was 34.8±14.4 years. During routine follow-up, 7.9% (n=27) of participants developed AVN, with a median diagnosis time of 15.2 (10.2-34.9) months after KT. In KTRs with AVN, the leading cause of ESRD was GN (52% vs. 20%, p<0.001). Preemptive transplantation, cadaveric transplantation, and induction therapies were similar between groups. RAAS inhibitor treatment rates are also similar between the two groups (%35 vs. %37, p=0.86). However, long-term follow-up revealed that patients with a history of AVN experienced significantly higher rates of rejection episodes compared to those without AVN (33% vs. 15%, p=0.01). The demographic and clinical characteristics were comparable across the study population, as detailed in Table 1.

AVN was diagnosed in 24 patients (89%), most commonly affecting the femoral head, 2 (7%) in the knee, and 1 (4%) in the humerus (Figure 1). After the diagnosis, corticosteroid therapy was discontinued in 52% of KTRs and reduced in 26%. Furthermore, 18 KTRs (67%) required surgical intervention at the affected sites due to AVN, while 2 (7%) underwent hyperbaric oxygen therapy. Treatment interventions against AVN are shown in Figure 2.

In univariate analysis, GN [odds ratio (OR):4.325, 95% confidence interval (CI), 1.936-9.661], cumulative steroid doses at post-transplant first year (OR: 1.001, 95% CI, 1.000-1.002) and rejection episodes (OR: 2.792, 95% CI, 1.185-6.578) detected as possible risk factors for AVN. Upon multivariate analysis, GN was identified as an independent risk factor for the development of AVN (OR: 4.373, 95% CI, 1.935-9.880; p<0.001) (Table 2).

Discussion

In this study, the prevalence of AVN among our KTRs was 7.9%. Patients with a history of AVN were found to have experienced more frequent rejection episodes; however, their long-term allograft survival rates were comparable. Moreover, our findings revealed that GN, the primary cause of ESRD, is an independent risk factor for the development of AVN. Our results may indicate the importance of close monitoring and tailored management strategies for high-risk KTRs, particularly those with GN as the underlying cause of ESRD.

Solid organ transplantation has become a cornerstone of modern medicine, advancing hope and enhancing the quality of life for individuals experiencing end-stage organ failure. The growing number of KTRs has brought to light new challenges, including post-transplant complications such as AVN. While the prevalence of AVN was reported as 24-40% in historical data, this rate is around 5% in current studies (4,13,14). Although its frequency is decreasing, our research emphasizes that AVN is still an important complication in KTRs. Also, the median diagnosis time of AVN in our cohort (15.2 months after KT) aligns with findings from prior studies, which have reported diagnosis timelines ranging from 12 to 24 months post-transplantation (7,15).

Besides, we found that AVN usually affected the femoral head, and 67% of KTRs with AVN required surgical interventions. One study reported that 83% of AVN cases required surgical treatment, and it is reminded that a substantial proportion

Table 1: Demographic characteristics and outcomes of kidney transplant recipients with avascular necrosis				
	Total n=343	**No AVN n=316 (92.1%)**	**AVN n=27 (7.9%)**	**p-value**
Age at transplantation (years)	34.8±14.4	35±14.7	32.4±11.7	0.87
Sex (female)	127 (37%)	116 (37%)	11 (41%)	0.67
DM, n (%)	37 (11%)	35 (11%)	2 (7%)	0.75
HT, n (%)	241 (70%)	220 (70%)	21 (78%)	0.37
ADPKD, n (%)	22 (6%)	22 (7%)	0 (0%)	0.15
GN, n (%)	77 (22%)	63 (20%)	14 (52%)	**<0.001**
NODAT, n (%)	58 (17%)	55 (17%)	3 (11%)	0.59
Smoking, n (%)	84 (25%)	74 (23%)	10 (37%)	0.11
Preemptive transplantation, n (%)	94 (27%)	83 (26%)	11 (41%)	0.10
Previous transplantation	24 (7%)	24 (8%)	0 (0%)	0.23
Cadaveric transplantation, n (%)	81 (24%)	73 (23%)	8 (30%)	0.44
Induction, n (%) **ATG** **Basiliximab** **None**	 140 (41%) 98 (29%) 105 (30%)	 129 (41%) 93 (29%) 94 (30%)	 11 (41%) 5 (18%) 11 (41%)	0.36
Delayed graft function, n (%)	34 (10%)	32 (10%)	2 (7%)	1.00
Immunosuppressive treatment **CNI, n (%)** **Antimetabolite, n (%)** **mTORi, n (%)**	 303 (88%) 293 (85%) 65 (19%)	 280 (87%) 269 (85%) 61 (19%)	 23 (85%) 24 (89%) 4 (15%)	 0.59 0.78 0.79
RAAS inhibitors, n (%)	122 (36%)	112 (35%)	10 (37%)	0.86
PTX before transplantation, n (%)	22 (6%)	20 (6%)	2 (7%)	0.68
Persistent HPT, n (%)	158 (46%)	142 (45%)	16 (59%)	0.15
Bisphosphonate, n (%)	28 (8%)	25 (8%)	3 (11%)	0.47
Total steroid dose at first year (mg)	3437±282	3429±270	3535±395	0.06
eGFR at baseline (mL/min/1.73 m²)	74 (60-97)	74 (61-97)	65 (55-102)	0.70
Proteinuria at baseline (mg/24h)	247 (160-408)	249 (156-406)	231 (185-511)	0.64
Rejection episode, n (%)	57 (17%)	48 (15%)	9 (33%)	**0.01**
Allograft lost, n (%)	50 (15%)	44 (14%)	6 (22%)	0.24
Follow-up time (months)	125.3±68.9	123±67.6	144.6±80.8	0.20

ADPKD: Autosomal dominant polycystic kidney disease, ATG: Anti-thymocyte globülin, CNI: Calcineurin inhibitör, DM: Diabetes mellitus, eGFR: estimated glomerular filtration rates, GN: Glomerulonephritis, HPT: Hyperparathyroidism, HT: Hypertension, mTORi: Mammalian target of rapamycin inhibitors, NODAT: New-onset diabetes after transplantation, PTX: Parathyroidectomy, RAAS: Renin angiotensin aldosteron system.

Table 2: Univariate and multivariate analysis of risk factors for the development of avascular necrosis				
	Univariate, OR (%95 CI)	**p-value**	**Multivariate, OR (%95 CI)**	**p-value**
Sex (Female)	0.844 (0.379-1.879)	0.67		
Age at transplantation	0.987 (0.960-1.015)	0.36		
GN	4.325 (1.936-9.661)	<0.001	4.373 (1.935-9.880)	**<0.001**
DM	0.642 (0.146-2.829)	0.55		
Smoking	1.924 (0.844-4.382)	0.11		
Preemptive transplantation	1.930 (0.861-4.328)	0.11		
Total steroid dose at first year	1.001 (1.000-1.002)	0.07	1.000 (0.999-1.002)	0.61
Rejection episode	2.792 (1.185-6.578)	0.02	2.395 (0.794-7.224)	0.12
Persistent HPT	1.782 (0.802-3.963)	0.15		

DM: Diabetes mellitus; GN: Glomerulonephritis, HPT: Hyperparathyroidism, OR: Odds ratio, CI: Confidence interval

of patients need surgery (6). The frequent need for surgical intervention in this vulnerable patient group is an important issue that needs to be underlined. A systematic review revealed that patients with solid organ transplants face significantly higher rates of acute kidney injury, cardiac complications, pneumonia, and surgical complications, such as transfusions and deep vein thrombosis following hip arthroplasty (16). Furthermore, these patients also exhibited notably higher rates of readmission and 90-day mortality.

Steroids are a key factor in the pathogenesis of AVN, with some studies indicating a strong association between both high cumulative doses and short-term high-dose exposures during rejection episodes and the occurrence of AVN (17). Although we examined total corticosteroid doses in the first year of KT, our study found no significant association with AVN. In line with our findings, some previous studies have not established a clear correlation between steroid dosage and AVN incidence (18,19). However, these results should be interpreted cautiously, considering the potential influence of confounding factors and variations in study methodologies. For instance, Khwaja et al. (20) implemented a maintenance protocol without long-term steroid use, involving a single intraoperative dose of MPZ (500 mg) and a short course of prednisone (1 mg/kg on the first postoperative day, tapered over four days and discontinued by day five). Within their cohort of 349 KTRs, they reported no cases of AVN (20).

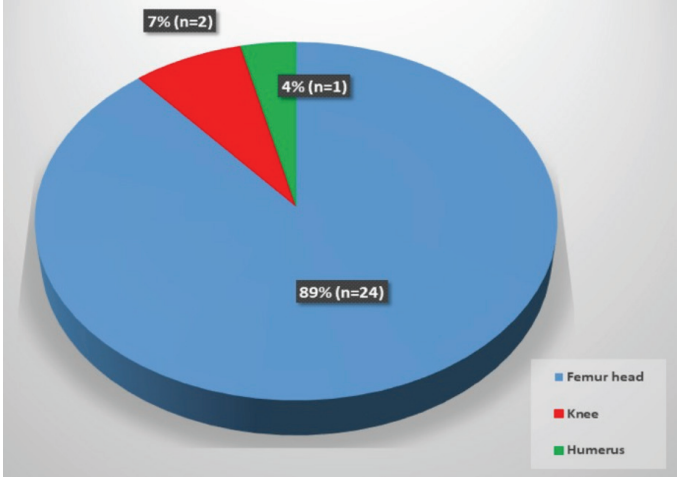

Figure 1: Site of avascular necrosis in kidney transplant recipients

Bone health in KTRs is a multifaceted issue influenced by pre-existing conditions such as renal osteodystrophy, secondary HPT, and adynamic bone disease (21). However, these bone lesions can also occur in patients with relatively preserved kidney function and are often unrelated to PTH levels. Our study suggests AVN may develop independently of traditional markers like serum PTH levels, parathyroidectomy before KT, or bisphosphonate medication. This findings highlight the complex interplay of factors contributing to post-transplant bone diseases, including pre-existing renal osteodystrophy and immunosuppressive therapy.

Previous studies have reported the critical role of the RAS in regulating bone marrow mesenchymal stem cells, which are vital for bone regeneration and remodeling, particularly in femoral head necrosis (22). RAS plays a key role in promoting angiogenesis by stimulating vascular endothelial growth factor (VEGF) production through angiotensin II, enhancing paracrine signaling, supporting cell survival, and facilitating bone repair (23). A reduction in angiogenesis, however, can impair nutrient and oxygen delivery to bone tissue, leading to demineralization, trabecular thinning, and, ultimately, structural collapse (24). Given that RAAS inhibitors are widely used to reduce proteinuria and prolong renal survival in KT recipients, these drugs may have an additive contribution to the development of AVN.

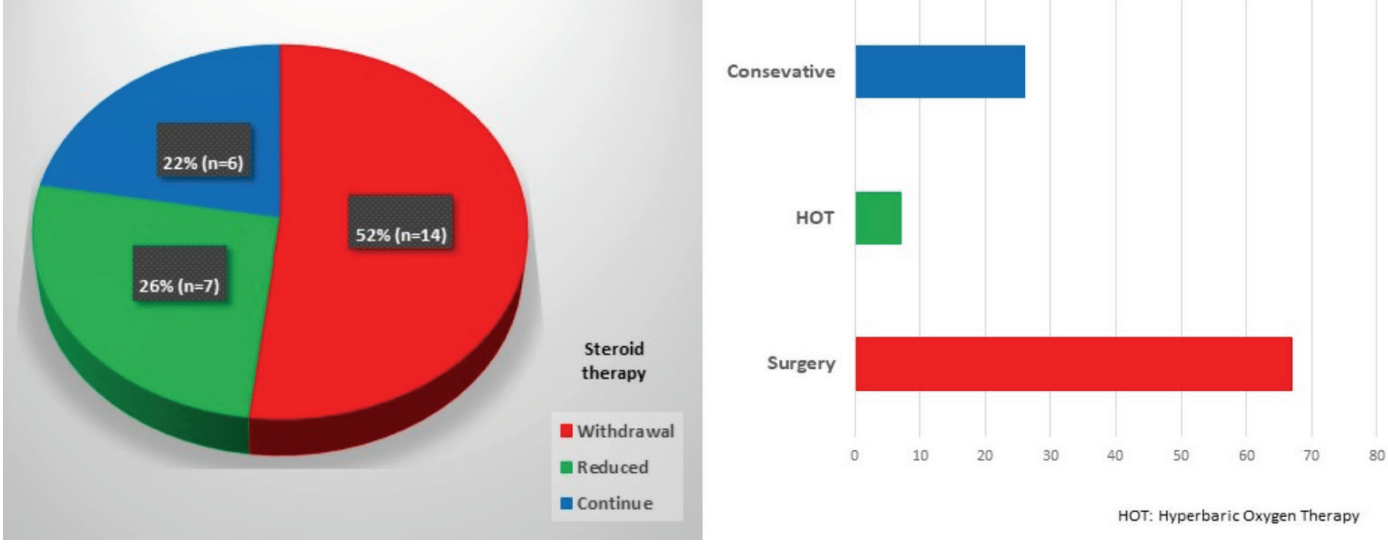

Figure 2 A-B: Treatment interventions for avascular necrosis in kidney transplant recipients

Nevertheless, we did not observe any correlation between RAS inhibitor treatment and the onset of AVN in our study.

Interestingly, our findings revealed that KTRs with GN as the primary cause of ESRD demonstrated an independent risk factor for AVN. This observation may be linked to prolonged pre-transplant steroid use and higher total cumulative steroid doses in these patients. Similar to our result, Schachtner et al. (6) reported that AVN incidence post-transplantation was higher in KTRs with ANCA vasculitis as the underlying disease. In addition, Yu et al. (25) compared 23 lupus patients with a history of KT to 94 matched controls. The results revealed a notably higher AVN rate in the lupus group (17.4% vs. 2.1%, p=0.04). The researchers concluded that the extended use of corticosteroids before transplantation may play a role in the development of AVN. The higher prevalence of AVN observed in this subgroup emphasizes the importance of closely monitoring steroid doses and considering immunosuppressive therapy strategies more carefully to minimize the risk of AVN.

Study Limitations

The study's limitations primarily stem from its retrospective and single-center design, which can significantly affect the validity and generalizability of the findings. Since the data is drawn from a single institution, the cohort might lack the diversity necessary to properly represent the broader patient population. Moreover, some missing values concerning human leukocyte antigen typing and patient weight hindered a comprehensive assessment of potential connections between these factors and AVN. While the chance of pre-existing or asymptomatic AVN cases is rare, it is a possibility that should be considered in the context of this study. Lastly, several possible confounding factors might have influenced the observed association between GN and AVN, such as the duration of the primary disease, the intensity of previous steroid therapy, and immunosuppressive therapies for the primary disease.

Conclusion

AVN is a debilitating bone disease that often causes significant functional impairment and reduces the quality of life in KTRs. Our study identified an association between GN underlying disease and an elevated risk of developing AVN. This increased incidence of AVN in patients with a history of GN may be linked to the prolonged use of steroid therapy prior to transplantation. Given the potential complications related to AVN, healthcare providers need to maintain heightened attention regarding the cumulative doses of steroids administered to these patients. Furthermore, an early discontinuation of steroid therapy may be a viable strategy for these vulnerable patients to reduce the risk of AVN. Future prospective studies are needed to investigate the benefits of steroid-sparing immunosuppressive protocols and examine the impact of GN on AVN.

Ethics

Ethics Committee Approval: Gazi University Ethics Committee approved the study protocol (protocol number: E-77082166-604.01-1148721, date: 21.01.2025).

Informed Consent: Informed consent was not required.

Footnotes

Authorship Contributions

Concept: Ö.F.A., O.H., G.G., Design: Ö.F.A., O.H., G.G., Data Collection and/or Processing: Ö.F.A., A.D., V.B.T., Analysis and/or Interpretation: Ö.F.A., O.H., G.G., Literature Search: Ö.F.A., A.D., V.B.T., Writing: Ö.F.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

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