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ORIGINAL ARTICLE

# Avascular necrosis in kidney transplant recipients: Incidence and risk factors in the modern immunosuppression era

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Pre-existing bone and mineral disorders, prolonged corticosteroid (CS) use, and predisposing comorbidities render kidney transplant recipients (KTRs) prone to bone complications, including avascular necrosis (AVN).[1] This complication, which diminishes the functional capacity of patients, may also be linked to heightened mortality rates in KTRs.[2] The pathogenesis of AVN arises from a combination of factors that disrupt blood flow to the bone, resulting in ischemia and subsequent bone necrosis.[3] The systemic nature of the underlying bone disease in non-traumatic AVN leads to lesion development in susceptible regions, notably the femoral head. Alongside alcohol use, obesity, male gender, and diabetes—recognized risk factors for

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## ABSTRACT

**Objectives:** This study aims to assess the incidence and risk factors for avascular necrosis (AVN) in kidney transplant recipients (KTRs) under modern immunosuppression.

**Patients and methods:** Between January 1993 and April 2023, a total of 769 KTRs (496 males, 273 females; mean age: 38.15±12.29 years) who underwent transplantation were retrospectively analyzed. The diagnosis of AVN was established using X-rays and magnetic resonance imaging to evaluate patients presenting with pain in one or more joints. Risk factors for AVN were analyzed in a cohort of 290 transplant recipients after 2007 under tacrolimus based treatment to standardize immunosuppression (178 males, 112 females; mean age: 40.6±12.0 years).

**Results:** The incidence of AVN was 8.2% (n=21) from 1993 to 2007 and 4.1% (n=21) from 2008 to 2023, retrospectively. The median duration from transplantation to the diagnosis of AVN was 15 (range, 1 to 68) months, with the femoral head being the predominant site affected. The reduction in AVN incidence, along with the replacement of cyclosporine by tacrolimus and the reduction in total corticosteroid dosage, was evident in recent era. The increased body mass index (BMI) (p=0.005), the onset of late acute rejection (p=0.024), and the administration of greater cumulative corticosteroid doses at both three (p=0.001) and 12 months (p<0.001) were correlated with the incidence of AVN in recipients undergoing tacrolimus-based maintenance immunosuppression. Multivariate analysis indicated that an elevated BMI (odds ratio [OR]=1.130, 95% confidence interval [CI]: 1.013-1.261; p=0.028) and a cumulative methylprednisolone dosage exceeding 4.5 g within 12 months (OR=12.692, 95% CI: 2.146-75.069; p=0.005) were significant predictors of AVN.

**Conclusion:** The incidence of AVN in kidney transplant recipients has significantly diminished in the modern immunosuppressive era and the elevated total corticosteroid dosage remains the principal risk factor for AVN among kidney transplant recipients. The implementation of preventive strategies and screening in high-risk populations should be coordinated between transplant specialists and orthopedic surgeons.

***Keywords:*** Avascular necrosis, body mass index, corticosteroids, immunosuppression, kidney transplantation.

AVN in the general population[3]—specific risk factors in the transplant population, including delayed graft function,[4] presence of acute rejection,[5,6] cytomegalovirus disease,[7] and genetic predisposition,[8-11] have also been identified.

Epidemiological studies indicate that KTRs display a markedly higher prevalence of AVN compared to the general population. The elevated risk is primarily attributed to the use of CS, which is prevalent in transplant populations owing to the necessity for immunosuppressive therapies. Recent studies have indicated a significant reduction in incidence to approximately 3 to 5%, explained by advancements in immunosuppressive therapies and decreased steroid dosages.[4,12,13] However, there are concerns that the incidence may be underestimated due to the initially asymptomatic presentation.[6,14]

Identifying high-risk patients, screening in the early post-transplant period and diagnosing the disease at initial stages are essential, as the prevention of AVN represents the primary objective. However, immunosuppression practices exhibit significant variability in studies investigating AVN risk factors, particularly due to modifications in immunosuppressive therapy post-2000s. In the present study, we aimed to determine the incidence and risk factors AVN in a recent cohort of KTRs, given the paucity of studies conducted under modern standard immunosuppression.

## PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ankara University Faculty of Medicine, Department of Nephrology between January 1993 and April 2023. A total of 769 KTRs (496 males, 273 females; mean age: 38.15±12.29 years) who were ≥18 years old and monitored for more than six months following transplantation at our transplant center were initially screened. The diagnosis of AVN was made through X-rays and magnetic resonance imaging (MRI) which were performed to assess patients reporting pain in one or more joints. The diagnosis and management of AVN were decided in collaboration with the local Orthopedics and Traumatology Department.

The incidence of AVN was evaluated separately for the periods 1993-2007 (n=256) and 2008-2023 (n=513), due to change in the maintenance immunosuppression approach between these periods. To identify the risk factors for AVN in patients under modern immunosuppression, individuals transplanted prior to 2008, those receiving immunosuppression other than the standard triple regimen of tacrolimus (TAC), mycophenolate (MPA), and CS, patients lacking post-transplant CS dosage data, and those with a pretransplant diagnosis of AVN were excluded. Finally a total of 290 patients with a mean age of 40.6±12.0 years and a male predominance (61.4%) were included in the risk factor analysis (Figure 1). The cohort was divided into two groups (n=290): 1-Post-transplant AVN-positive (n=21, 7.2%) 2-Post-transplant AVN-negative (n=269, 92.8%).

Primary kidney disease, comorbidities, dialysis vintage, body mass index (BMI), pretransplant immunological risk, acute rejection history, infectious complications, graft outcomes and patient survival were evaluated from medical records. The cumulative CS dose over one-year post-transplantation for all patients, as well as the cumulative steroid dose administered until the diagnosis of AVN in the AVN group, were quantified in terms of methylprednisolone equivalents. Serum creatinine (Scr), estimated glomerular filtration rate (eGFR), serum calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), and parathormone (PTH) were recorded at postoperative period. Written informed consent was obtained from each patient. The study protocol was approved by the Ankara University Clinical Research Ethics Committee (Date: 14.01.2025, No: İ11-891-24). The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Immunosuppressive treatment regimen

The immunological risk of KTRs was evaluated based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Induction therapy, utilizing anti-thymocyte globulin or implemented administered in alignment with these guidelines.[15] Following a pulse of methylprednisolone (500 mg daily for three days), a dosage of 1 mg/kg/day was given for an additional three days, after which the methylprednisolone dose was decreased by 8 mg every three days until reaching 24 mg. The dosage was decreased to 4 mg by the end of the third month. Triple maintenance immunosuppression regimen was consisted of CS, calcineurin inhibitor, and antiproliferative agent. Methylprednisolone (500 mg daily for three days) treatment was applied to cases who experienced acute rejection, and additional treatment was added according to the classification of rejection determined by allograft biopsy.

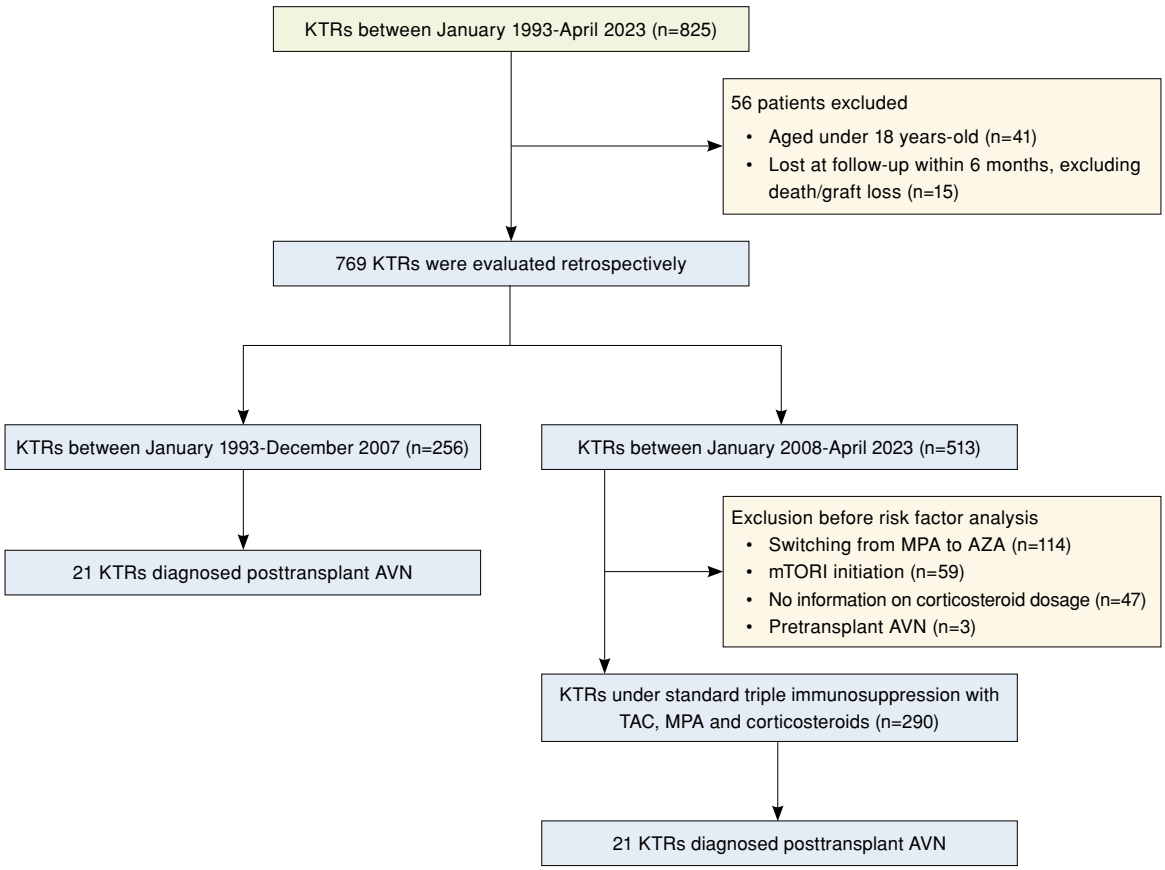



**FIGURE 1.** Study flowchart.
KTRs: Kidney transplant recipients; MPA: Mycophenolate; AZA: Azatiopurine; mTORi: Mammalian target of rapamycin inhibitor; AVN: Avascular necrosis; TAC, tacrolimus.

### Statistical analysis

Statistical analysis was performed using the IBM SPSS version 27.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. Comparisons between the groups were performed utilizing the Mann-Whitney U test for continuous variables, while chi-square or Fisher exact tests were employed for categorical variables. The primary outcome of the study was the development of AVN, and the secondary outcome involved identifying risk factors for AVN in the context of modern immunosuppression. Multivariate logistic regression analyses identified independent predictors of AVN. Variables exhibiting a p-value less than 0.25 in univariate analyses were incorporated into the models. The evaluation of model performance was conducted applying the Nagelkerke $R^2$ and the Hosmer-Lemeshow goodness-of-fit test. The final model was established using a backward stepwise elimination approach, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated for each variable. A $p$ value of $<0.05$ was considered statistically significant.

## RESULTS

### Characteristics of post-transplant AVN

Among whole cohort, three patients (0.4%) had pre-transplant AVN and 42 (5.5%) were diagnosed post-transplant AVN. The incidence of AVN was decreased from 8.2 to 4.1% between the periods 1993-2007 (n=21) and 2008-2023 (n=21). The comparison of the characteristics of AVN patients between the two periods is given in Table I. The median time to AVN diagnosis post-transplantation was 15 (range, 1 to 68) months, and 83.3% of the patients were diagnosed within first two years after transplantation. The mean recipient age at the time of transplant was 39.2±11.6 years, with a male predominance (n=35, 85.4%). The femoral head

**TABLE I**
Demographic and clinical data of patients with posttransplant avascular necrosis (n=42)

| Parameters | AVN, 1993-2007 (n=21) | | | | | AVN, 2008-2023 (n=21) | | | | | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | Mean±SD | Median | Min-Max | n | % | Mean±SD | Median | Min-Max | |
| Recipient age at Tx (year) | | | 37.6±10.1 | | | | | 40.8±13.1 | | | 0.381 |
| Recipient sex, male | 18 | 85.7 | | | | 17 | 81.0 | | | | 1.000 |
| Preemptive Tx | 0 | 0 | | | | 5 | 23.8 | | | | 0.058 |
| Dialysis vintage (mo) | | | | 18 | 6-96 | | | | 56 | 6-216 | 0.077 |
| Body mass index (kg/m$^2$) | | | 32.8±9.9 | | | | | 33.7±8.6 | | | 0.817 |
| Deceased donor | 3 | 14.3 | | | | 6 | 28.6 | | | | 0.277 |
| HLA mismatch number | | | | 2 | 0-4 | | | | 3 | 1-6 | **0.002** |
| Induction therapy | | | | | | | | | | | 0.085 |
| None | 16 | 76.2 | | | | 9 | 42.9 | | | | |
| Basiliximab | 2 | 9.5 | | | | 10 | 47.6 | | | | |
| Anti-thymocyte immunoglobulin | 3 | 14.3 | | | | 2 | 9.5 | | | | |
| Initial maintanence immunosuppression | | | | | | | | | | | **<0.001** |
| CS+AZA+CSA | 15 | 71.4 | | | | 0 | 0 | | | | |
| CS+MPA+CSA | 2 | 9.5 | | | | 0 | 0 | | | | |
| CS+MPA+TAC | 4 | 19.0 | | | | 21 | 100.0 | | | | |
| Cumulative corticosteroid dosage (g) | | | | | | | | | | | |
| Posttransplant 3 months | | | | 4090 | 2890-8280 | | | | 3235 | 1800-5470 | **0.012** |
| Posttransplant 12 months | | | | 6200 | 4170-14500 | | | | 4535 | 2300-12370 | 0.055 |
| Until AVN diagnosis | | | | 20665 | 4170-53580 | | | | 9380 | 2300-27770 | **0.016** |
| Posttransplant medical complications | | | | | | | | | | | |
| Acute rejection, first year | 9 | 42.9 | | | | 3 | 25.0 | | | | **0.040** |
| Acute rejection, late | 0 | 0 | | | | 2 | 10.0 | | | | 0.232 |
| Cytomegalovirus infection | 5 | 23.8 | | | | 3 | 14.3 | | | | 0.451 |
| BK viremia | 0 | 0 | | | | 4 | 19.0 | | | | 0.295 |
| eGFR, 12$^{th}$ month (CKD-EPI, mL/dk/1.73 m$^2$) | | | 58.8±21.1 | | | | | | | 78.7±21.8 | **0.005** |
| **Characteristics of AVN** | | | | | | | | | | | |
| Posttransplant diagnosis time (mo) | | | | 17 | 2-60 | | | | 14 | 1-68 | 0.512 |
| Site of AVN | | | | | | | | | | | 1.000 |
| Femoral head | 21 | 100.0 | | | | 20 | 95.2 | | | | |
| Knee | 0 | 0 | | | | 1 | 4.8 | | | | |
| Humerus | 0 | 0 | | | | 1 | 4.8 | | | | |
| Bilateral AVN of femoral head | 8 | 38.1 | | | | 10 | 47.6 | | | | 0.877 |
| Treatment of AVN | | | | | | | | | | | |
| Corticosteroid reduction/discontinuation | 14 | 66.6 | | | | 17 | 80.1 | | | | 0.393 |
| Operative | 13 | 61.9 | | | | 6 | 28.5 | | | | **0.073** |
| Core decompression | 5 | 23.8 | | | | 5 | 23.8 | | | | |
| Total arthroplasty | 8 | 38.1 | | | | 1 | 4.8 | | | | |

SD: Standard deviation; AVN: Avascular necrosis; Tx: Transplantation; HLA: Human leucocyte antigen; CS: Corticosteroid; AZA: Azathiopurine; CSA: Cyclosporine; MPA: Mycophenolate; TAC: Tacrolimus; eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic kidney disease epidemiology collaboration; Bold: p<0.05.

**TABLE II**

Demographic and clinical data of recipients in 2008-2023, according to posttransplant avascular necrosis status (n=290)

| | AVN-negative (n=269, 92.8%) | | | | | AVN-positive (n=21, 7.2%) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Parameters | n | % | Mean±SD | Median | Min-Max | n | % | Mean±SD | Median | Min-Max | *p* |
| Recipient age at Tx (year) | | | 40.6±12.0 | | | | | 40.8±13.1 | | | 0.920 |
| Recipient sex | | | | | | | | | | | |
| Male | 161 | 59.9 | | | | 17 | 81.0 | | | | 0.056 |
| ESKD etiology | | | | | | | | | | | 0.276 |
| Hypertension | 37 | 13.8 | | | | 7 | 33.3 | | | | |
| Glomerulonephritis | 73 | 27.1 | | | | 3 | 14.3 | | | | |
| Diabetes mellitus | 31 | 11.5 | | | | 1 | 4.8 | | | | |
| TIN+VUR+ON+PN | 35 | 13.0 | | | | 1 | 4.8 | | | | |
| Other | 38 | 14.1 | | | | 5 | 23.8 | | | | |
| Unknown | 55 | 20.4 | | | | 4 | 19.0 | | | | |
| Preemptive Tx | 91 | 33.8 | | | | 5 | 23.8 | | | | 0.604 |
| Dialysis vintage (mo) | | | | 12 | 1-375 | | | | 56 | 6-216 | 0.066 |
| Comorbidities | | | | | | | | | | | |
| Diabetes mellitus | 37 | 13.8 | | | | 2 | 9.5 | | | | 0.750 |
| Hypertension | 167 | 62.1 | | | | 16 | 76.2 | | | | 0.291 |
| Cardiovascular disease | 14 | 5.2 | | | | 1 | 4.8 | | | | 0.609 |
| Body mass index (kg/m$^2$) | | | 27.9±8.4 | | | | | 33.7±8.6 | | | **0.004** |
| Deceased donor | 51 | 19.0 | | | | 6 | 28.6 | | | | **0.035** |
| HLA mismatch number | | | | 3 | 0-6 | | | | 3 | 1-6 | 0.232 |
| Anti-HLA antibody positivity* | 89 | 33.1 | | | | 5 | 23.8 | | | | 0.392 |
| Induction therapy | | | | | | | | | | | 0.549 |
| None | 91 | 33.8 | | | | 9 | 42.9 | | | | |
| Basiliximab | 143 | 53.2 | | | | 10 | 47.6 | | | | |
| ATG | 35 | 13.0 | | | | 2 | 9.5 | | | | |
| Cumulative methylprednisolone dosage (g) | | | | | | | | | | | |
| Posttransplant 3 months | | | | 2638 | 750-5680 | | | | 3235 | 1800-5470 | **<0.001** |
| >3 g | 66 | 24.5 | | | | 13 | 61.9 | | | | **0.001** |
| Posttransplant 12 months | | | | 3732 | 2520-8010 | | | | 4535 | 2300-12370 | **0.020** |
| >4.5 g | 42 | 15.6 | | | | 12 | 57.1 | | | | **<0.001** |
| Laboratory data at Tx | | | | | | | | | | | |
| Ca (mg/dL) | | | 8.3±1.1 | | | | | 8.5±1.1 | | | 0.889 |
| P (mg/dL) | | | 4.9±1.5 | | | | | 5.2±1.3 | 431.0 | 50.8-919 | 0.780 |
| PTH (pg/mL) | | | | 395.9 | 15.0-2425.7 | | | | 72 | 57-239 | 0.371 |
| ALP (U/L) | | | | 89 | 32-1453 | | | | | | 0.357 |
| Laboratory data at 3$^{rd}$ month post Tx | | | | | | | | | | | |
| Ca (mg/dL) | | | 9.7±0.7 | | | | | 10.1±0.6 | | | **0.027** |
| P (mg/dL) | | | 3.2±0.8 | | | | | 3.0±0.6 | | | 0.340 |
| PTH (pg/mL) | 85 | | | 105.0 | 6.1-2831.4 | | | | 67.2 | 47.5-397 | 0.508 |
| ALP (U/L) | | | | 89 | 32-1453 | | | | 75 | 36-202 | 0.920 |
| eGFR, (CKD-EPI, mL/dk/1.73 m$^2$) | | | 72.6±23.1 | | | | | 80.9±25.8 | | | 0.085 |
| Posttransplant medical complications | | | | | | | | | | | |
| Acute rejection, first year | 38 | 14.1 | | | | 3 | 14.3 | | | | 1.000 |
| Acute rejection, late | 3 | 1.1 | | | | 2 | 9.5 | | | | 0.052 |
| Cytomegalovirus infection | 28 | 10.4 | | | | 3 | 14.3 | | | | 0.656 |
| BK viremia | 41 | 15.2 | | | | 4 | 19.0 | | | | 0.529 |
| Posttransplant follow-up duration (mo) | | | 73.0±39.5 | | | | | 111.1±49.6 | | | <0.001 |

AVN: Avascular necrosis; Tx: Transplantation; ESKD: End stage kidney disease; TIN: Tubulointerstitial nephritis; VUR: Vesicoureteral reflux; ON: Obstructive nephropaty; PN: Pyelonephritis; HLA: Human leucocyte antigen; ATG: Anti-thymocyte immunoglobulin; PTH: Parathormone; ALP: Alkaline phosphatase; eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic kidney disease epidemiology collaboration; * Anti-HLA antibody included either anti-HLA class I or class II or both; Bold: p<0.05.

remained the most common site of involvement in both groups, although in the 2008-2023 group knee (n=1) and humerus (n=1) were involved in two patients. Bilateral AVN of the femoral head was common in both cohorts (n=18, 42.9%). In addition, CS treatment was reduced or discontinued in 73.8% (n=31) of patients, and approximately half of them (n=19, 45.2%) required surgical intervention. Surgery rates appeared to be decreasing in recent years (p=0.073). Among patients who underwent surgery, total hip arthroplasty was performed on nine individuals, while 10 patients were treated with core decompression, including two cases that combined with vascularized bone grafting. The incidence of total hip arthroplasty was elevated in the earlier period. However, no significant differences were noted in surgical method preferences related to the timing of diagnosis or the total CS dosage. None of the patients experienced postoperative deep vein thrombosis.

A significant change in immunosuppressive practices was observed between eras. In the 1993-2007 cohort, initial maintenance immunosuppression consisted mainly of CS, azathioprine (AZA), and cyclosporine (CSA). In contrast, all patients in the 2008-2023 cohort received CS, MPA, and TAC (p<0.001). Use of basiliximab for induction increased markedly (47.6% *vs.* 9.5%, p=0.004), and fewer patients in the recent group received no induction therapy (42.9% *vs.* 76.2%, p=0.085). Cumulative CS exposure was significantly lower in the 2008-2023 group at three months (3,235 *vs.* 4,090 g methylprednisolone, p=0.012), and until AVN diagnosis (9,380 *vs.* 20,665 g methylprednisolone, p=0.016).

**Risk factors of post-transplant AVN under modern immunosuppression**

There were no statistically significant differences in the mean recipient age at the time of transplantation (40.8±13.1 *vs.* 40.6±12.0 years, p=0.920) or sex distribution according to AVN status, although male sex was more common among those with AVN (81.0% *vs.* 59.9%, p=0.056) (Table II). Patients who developed AVN had a longer dialysis duration prior to transplantation (median 56 months [6-216] *vs.* 12 months [1-375], p=0.066). Dialysis modality, preemptive transplantation, end-stage kidney disease (ESKD) etiology, comorbidities were similar between groups. Notably, the mean BMI was markedly greater in patients with AVN (33.7±8.6 *vs.* 27.9±8.4 kg/m², p=0.004), and the proportions of patients with BMI ≥25 kg/m² (71.4% *vs.* 52.0%, p=0.049) and BMI ≥30 kg/m² (66.7% *vs.* 32.3%, p=0.001) were both significantly greater. Deceased donor grafts were more frequent in the AVN group (28.6% *vs.* 19.0%, p=0.035). No significant differences were detected in rates of re-transplantation, the use of pretransplant immunosuppression, human leukocyte antibody (HLA) mismatch number, anti-HLA antibody status and the type of induction therapy. The incidence of post-transplant complications, including acute rejection, cytomegalovirus infection and BK viremia, were comparable between the groups.

Examination in terms of bone-mineral disease displayed that serum Ca, P, PTH and ALP levels were similar at the time of transplantation; however, serum Ca levels were significantly higher in the

**TABLE III**

Univariate and multivariate logistic regression analyses of risk factors for association with post-transplant avascular necrosis (n=290)

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Parameters | OR | 95% CI | *p* | OR | 95% CI | *p* |
| Sex | | | | | | |
| Male | 2.851 | 0.934-8.702 | 0.066 | 3.558 | 0.447-28.312 | 0.230 |
| Increased dialysis vintage | 1.007 | 0.999-1.015 | 0.080 | 1.009 | 0.998-1.019 | 0.105 |
| Increased BMI | 1.069 | 1.020-1.121 | **0.005** | 1.130 | 1.013-1.261 | **0.028** |
| Increased HLA mismatch number | 1.222 | 0.879-1.699 | 0.232 | 1.563 | 0.857-2.853 | 0.145 |
| Acute rejection, after 1st year | 8.481 | 1.330-54.071 | **0.024** | 22.456 | 0.950-530.967 | 0.054 |
| Cumulative methylprednisolone dose >3 g at 3rd month | 5.177 | 1.981-13.534 | **0.001** | 0.718 | 0.026-19.970 | 0.845 |
| Cumulative methylprednisolone dose >4.5 g at 12th month | 7.393 | 2.847-19.195 | **<0.001** | 12.692 | 2.146-75.069 | **0.005** |

OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; HLA: Human leucocyte antigen. For multivariate analyses all variables were included in the model. bold=p<0.05.

AVN group three months after transplantation (10.1±0.6 *vs.* 9.7±0.7 mg/dL, p=0.027). Cumulative CS exposure was significantly greater among patients with AVN at both three months (3,235 mg [1,800-5,470] *vs.* 2,638 mg [750-5,680] methylprednisolone, p<0.001) and 12 months (4,535 mg [2,300-12,370] *vs.* 3,732 mg [2,520-8,010] methylprednisolone, p=0.020) post-transplantation.

In the multivariate analysis, two variables emerged as independent risk factors (Table III). Increased BMI was significantly related with a higher risk of AVN (OR=1.130, 95% CI: 1.013-1.261; p=0.028). Similarly, a cumulative methylprednisolone dose greater than 4.5 g at 12 months post-transplantation was strongly associated with AVN (OR=12.692, 95% CI: 2.146-75.069; p=0.005). Although acute rejection episodes occurring after the first post-transplant year showed a substantial effect size (OR=22.456, 95% CI: 0.950-530.967), the association did not reach statistical significance (p=0.054). Other variables, including male sex, increased dialysis vintage, higher HLA mismatch number, and cumulative CS dose greater than 3 g at three months, were not significantly associated with AVN in the multivariate model.

## DISCUSSION

In the present study, we determined the incidence and risk factors for AVN in recent kidney transplant cohort under modern immunosuppression. The main finding of this study is that the incidence of post-transplant AVN has decreased from 8.2 to 4.1% in the modern immunosuppression era, probably attributable to reduced steroid use. Additionally, factors associated with AVN risk include elevated BMI and increased cumulative CS dose.

In a previous study conducted at our center 19 out of 243 patients (7.8%) who were transplanted between 1993 and 2006 were diagnosed AVN.[8] A recent study in Türkiye reported the incidence of AVN 9.7% in 360 kidney transplant patients between 2005 and 2021.[7] The fact that our recent rate of 4.1% is lower than these and is similar to incidences reported in recent studies can be explained by changes in immunosuppressive therapy and management practices of KTRs.[4,12,13,16]

Our patients were mostly diagnosed AVN within the first two years after transplantation after presenting with symptoms. Considering the delay between the onset of symptoms and the diagnosis of AVN,[13] it is of utmost importance for the clinician to better evaluate the symptoms. Marston et al.[14] screened KTRs for AVN with MRI within six months after transplantation and every four months and thereafter. They recommended MRI screening one-year post-transplantation due to an 11% incidence of AVN of the femoral head diagnosed within 10 months following the transplant. However, a more recent prospective single-center study which performed MRI at six months after kidney transplantation determined a 3.1% incidence of AVN of femoral head in patients.[17] This indicates that risk factors can be meticulously assessed and screening may be planned accordingly. Therefore, coordination between transplant specialists and orthopedic surgeons is essential for the early diagnosis and management.

Increased cumulative CS dose, particularly in the early period after transplantation, is a risk factor for AVN,[4,6,18,19] although some studies found no relationship.[8,12,17] Recently, Kaya et al.[7] demonstrated that a total steroid dose of >4 g in the first three months increased the risk of developing AVN 4-fold.[7] In our study a correlation between escalating CS dosage and the incidence of post-transplant AVN was identified, noting that a cumulative methylprednisolone dose above 4.5 g within one year enhanced the risk of AVN by 12.7 times. The relationship between the increasing cumulative dose and duration of treatment of CS and the risk of AVN has been demonstrated not only in transplantation and autoinflammatory diseases,[20] but also in patients with severe acute respiratory syndrome and coronavirus disease 2019 in the pandemic recently experienced.[21,22] The effect of CS on apoptosis, coagulation, lipid metabolism, endothelial cell damage plays a role in the development of AVN.[23] A study of 765 KTRs between 2001 and 2013 reported the incidence of AVN of 4.1% at 10 years after transplantation and the rate of AVN development was higher in patients using CSA (8.0%) compared with those using TAC (2.7%).[12] The reduction in AVN incidence, that have also been demonstrated under TAC-based immunosuppression in our study, may be explained by the reduction in acute rejection incidence and total CS dose with the use of TAC in immunosuppression.[24] The incidence of femoral head AVN in KTRs decreased from 7.2 to 1.1% following the implementation of steroid minimization protocols.[16] Although there was a reduction in steroid use, an increased risk of AVN was linked to steroid administration, while MPA was associated with a decreased risk. Felten et al.[13]

reported the incidence of post-transplant AVN to be 0.6% at one year, 1.5% at two years, and 2.2% during follow-up; which is one of the lowest incidences noted. Consistent with our findings, overweight status and higher cumulative CS doses were significantly related to the presence of AVN in this French cohort. After adjusting for cumulative steroid dosages, HLA mismatch number, pre-transplant P, and Ca × P levels were found to be risk factors for AVN.[17] However, secondary hyperparathyroidism was not identified as a risk factor in our study.

Elevated BMI has been identified as a potential risk factor for the onset of AVN in KTRs. Excess adiposity can lead to microvascular dysfunction, elevated intraosseous pressure, and modified lipid metabolism, which may impair bone perfusion and increase the risk of ischemic bone necrosis.[3,25] Obesity is frequently linked to metabolic complications and heightened inflammatory responses, which may further increase bone susceptibility during immunosuppressive treatment. Numerous studies indicate a positive correlation between increased BMI and the occurrence of post-transplant AVN, underscoring the importance of meticulous weight management before and after transplantation as a component of comprehensive strategies to mitigate AVN risk.[10,13] The growing prevalence of obesity among KTRs, similar to that observed in the general population, underscores the significance of this risk factor.[26]

The initial stages of AVN can be managed through conservative approaches, including weight-bearing restrictions, medications, and physical rehabilitation.[27] The reduction or early withdrawal of CS is an efficient preventive measure for AVN. However, AVN is a primary indication for total hip arthroplasty, particularly in advanced stages of the condition.[28] Of note, KTRs have a significantly lower rates of postoperative medical and surgical complications, emergency department visits, and hospital readmission compared to end-stage kidney disease patients.[29] Nevertheless, due to the elevated risk of postoperative deep vein thrombosis compared to the controls with no transplantation history, greater emphasis for deep vein thrombosis prevention is crucial.[30]

The primary strength of this study lies in its examination of risk factors among patients undergoing uniform immunosuppression in contemporary practice, as immunosuppressive treatment methods exhibit considerable variability across studies in the literature. However, this study has certain limitations. The small sample size and retrospective design of the study may allow for residual confounding. The relationship between alcohol consumption, dyslipidemia, and hypercoagulability with AVN was not assessed. The hazard ratio for acute rejection had a wide confidence interval, indicating high variability and potential imprecision, and should be interpreted cautiously. Furthermore, since AVN was diagnosed with MRI after symptoms developed, some asymptomatic AVN cases might have been overlooked. Initially asymptomatic presentation might have led to a lower incidence. The retrospective design of the study precluded re-evaluation of patients' diagnostic procedures at the time of AVN diagnosis.

In conclusion, our study results emphasize high BMI and high-dose CS exposure as significant modifiable risk factors, despite a decreasing incidence of AVN in KTRs in modern immunosuppression era. Increased awareness among transplant specialists and orthopedic surgeons is essential due to the impact of AVN on patient quality of life and long-term outcomes. Clinicians should screen high-risk groups for early diagnosis of AVN and optimize preventive strategies, including careful monitoring, specific immunosuppressive protocols, and lifestyle modifications.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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