RESEARCH ARTICLE

Profile of avascular necrosis cases among kidney transplant recipients on a low-dose steroid regimen, A Retrospective Study

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Abstract

Objective: To assess the clinical profile, biochemical parameters and outcomes of kidney transplant recipients who developed avascular necrosis while on a low-dose steroid regimen.

Method: The descriptive, retrospective cross-sectional study was conducted from January to December 2022 at the Renal Transplant Unit of the Dow University of Health Sciences, Karachi, and comprised data on kidney transplant recipients diagnosed with avascular necrosis between March 2017 and December 2022. Data on demographics, biochemical markers, steroid protocols, joint involvement, diagnostic techniques, rejection episodes and surgical interventions was collected. Data was analysed using SPSS 27.

Results: Of the 30 patients, 21(70%) were males and 9(30%) were females. The overall mean age was 37.23±8.62 years (range: 24-60 years). Avascular necrosis diagnosis was confirmed by magnetic resonance imaging scan in 28(93.3%) cases. Surgical intervention was required in 8(26.7%) patients. Rejection episodes were 16(53.3%) in the first six months, while 14(46.7%) developed avascular necrosis without prior rejection (p=0.689). A significant correlation was observed between gender and surgical intervention, with females more likely to require surgery compared to males (p=0.032).

Conclusion: Female patients showed a higher likelihood of requiring surgical management, highlighting the importance of gender-sensitive orthopaedic monitoring post-transplant.

Key Word: Avascular necrosis, Kidney transplant, Low-dose steroid, Surgical intervention, Orthopaedic outcomes.

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Introduction

Osteonecrosis, another name for avascular necrosis (AVN), is a crippling disease in which bone tissue dies as a result of a disrupted blood supply. It mostly affects weight-bearing joints, particularly the hip[1], and it can cause severe functional disabilities and gradual joint deterioration. Immunosuppressive treatment, especially corticosteroids, is the main cause of AVN, a well-known side-effect among kidney transplant recipients.[2]

Although corticosteroids are essential for avoiding graft rejection, prolonged use of them is linked to a number of negative side-effects, such as AVN, osteoporosis and bone-loss. In the past, high-dose steroid regimens were commonplace, which led to a rise in AVN incidence among transplant recipients. Modern immunosuppressive protocols, however, have changed to low-dose or steroid-sparing regimens in response to these worries. The goal is to lessen the burden of steroid-related problems without sacrificing graft survival. High-dose corticosteroid pulses are frequently required during episodes of acute graft rejection, which may raise the risk of AVN even in patients receiving otherwise moderate maintenance doses.[3] The difficulty of striking a balance between immunosuppression and unfavourable musculoskeletal consequences is highlighted by this connection.

Although low-dose steroid regimens have been widely used, post-transplant patients continue to experience AVN, which raises concerns about how effective dose reduction is in preventing this complication.[4] Because of its great sensitivity in identifying early-stage AVN, magnetic resonance imaging (MRI) has emerged as the go-to diagnostic tool.[5] There is still a lack of clarity on the precise burden, clinical manifestation, and therapeutic profile of AVN in individuals on low-dose steroids. Moreover, there is a dearth of information tailored to kidney transplant recipients in countries with low resources.

The current study was planned to assess the clinical profile, biochemical parameters and outcomes of kidney transplant recipients who developed AVN while on a low-dose steroid regimen in a low-resource environment.

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Materials and Methods

The retrospective descriptive, cross-sectional study was conducted from January to December 2022 at the Renal Transplant Unit of the Dow University of Health Sciences (DUHS), Karachi, and comprised data on kidney transplant recipients diagnosed with AVN between March 2017 and December 2022. After exemption from the institutional ethics review board, patients were identified from medical records and outpatient follow-up clinics. Both male and female post-transplant patients, irrespective of the duration since transplantation, were included if they had a radiologically confirmed diagnosis of AVN. The sample was raised consecutively based on AVN diagnosis among kidney transplant recipients.

Every patient was following a typical low-dose steroid therapy as part of their immunosuppressive post-transplant programme. A total of 500mg methylprednisolone was administered intraoperatively as the induction dose, followed by 0.5mg/kg/day for 1 month which was tapered to 5mg/day till the end of the third month. The maintenance dose was 5mg/day of oral prednisolone. According to the institutional protocol, mycophenolate mofetil and calcineurin inhibitors (tacrolimus/cyclosporine) were additional immunosuppressive medications.

After taking informed consent from the patients, data was collected, including demographic variables, biochemical markers at baseline and post-transplant, including parathyroid hormone (PTH), calcium and phosphorus. Steroid exposure of each patient was noted. AVN characteristics included joint involvement, diagnostic modality (MRI or X-ray). Data was also noted regarding surgical intervention, and post-transplant complications, including rejection episodes, in the preceding six months.

The patients who had undergone a second kidney transplant, had less than one year of haemodialysis before transplant, were younger than 18 or older than 60 years, or had received a non-related renal transplant were excluded. Additionally, menopausal females, patients with pathological fractures, those who experienced transplant rejection within the first six months, and individuals with pre-transplant parathyroid hormone (PTH) levels greater than 500 pg/mL were excluded from the study.

Data was analysed using SPSS 27. Descriptive statistics were calculated for central tendency and dispersion. Continuous variables were expressed as mean ± standard deviation, while categorical variables were reported as frequencies and percentages. Data normality was tested using the Shapiro-Wilk test. It showed skewed distribution of PTH, and normal distribution of calcium and phosphorus. Wilcoxon Signed-Rank test was used to compare bassline and post-transplant PTH. Chi-square test was used to assess the relationship between rejection history and surgical intervention. Fisher's Exact test was used where appropriate. $P<0.05$ was considered significant.

Results

Of the 600 transplant patients, 30(5%) developed AVN involving the hip joint. Of them, 21(70%) were males and

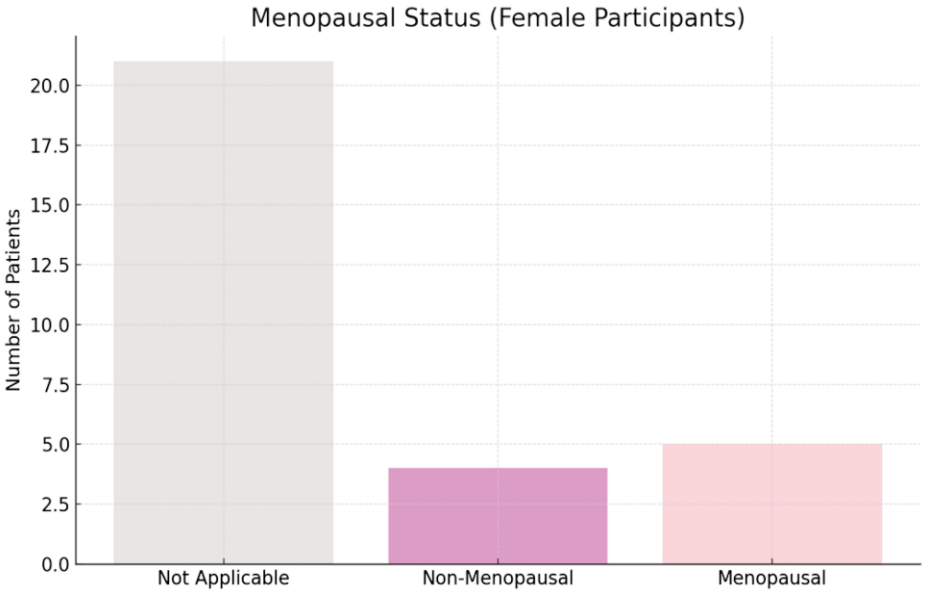

Figure: Menopausal status.

Table- Biochemical parameters.

Parameter	Pre-Transplant (Mean ± SD)	Range	Post-Transplant (Mean ± SD)	Range	P Value
Parathyroid Hormone (PTH)	403.65 ± 329.16 pg/mL	129 – 1900 pg/mL	84.34 ± 65.78 pg/mL	10 – 311 pg/mL	p<0.001
Calcium	8.44 ± 0.72 mg/dL	6.7 – 9.9 mg/dL	8.95 ± 0.63 mg/dL	7.8 – 10.5 mg/dL	p>0.05
Phosphorus	5.94 ± 2.23 mg/dL	2.21 – 11.0 mg/dL	3.92 ± 1.47 mg/dL	1.4 – 8.0 mg/dL	p=>0.05

SD: Standard deviation.

9(30%) were females. The overall mean age was 37.23±8.62 years (range: 24-60 years). Overall, 8(26.6%) patients had AVN stage 4-5 and required surgical interventions of hip joints, with 6(20%) having core decompressions, and 2(6.67%) having fibular graft placements. The remaining 22(73.33%) patients had AVN stages 1-3, and did not require any surgical intervention and were managed successfully with conservative measures, including physical therapy, weight reduction and pain relief. Among the female participants, 5(16.7%) were postmenopausal (Figure 1). MRI was the diagnostic modality in 28(93.3%) cases, while X-ray was used in 2(6.7%) cases. A total of 16(53.3%) patients had experienced rejection episodes within the preceding six months. There was no significant association between rejection history and the need for surgical intervention (p=0.689).

All the biochemical markers successfully normalised post-transplant, and the difference was significant for PTH (Table).The loading dose of steroid was consistent in all the cases. It was 6.6mg/kg methylprednisolone, while the maintenance therapy consisted of 0.5mg/kg/day. Graft rejection cases necessitated a pulse therapy of methylprednisolone of up to 20mg/kg combined with other anti-rejection agents, including anti-thymocyte globulin (ATG), intravenous immunoglobulin (IVIG) and plasmapheresis.

Discussion

The current study gives an outline of the clinical and biochemical properties of renal transplant recipients who suffered AVN while they were maintained on a low-dose steroid regimen. All cases of AVN involved the hip joint, with MRI being the primary diagnostic modality. . Among other findings, no significant association was found between gender and rejection episodes, which was in line with evidence indicating that gender may not independently influence the risk of rejection in kidney transplant recipients.[6]

The current study focussed on AVN instances among kidney transplant recipients who were being treated with low-dose steroid regimens, a population that has generally remained underreported. A thorough profile of this high-risk population was facilitated by the cross-sectional design which allowed for the collection of several clinical and biochemical markers at one time point.[7]

Expected limits must be taken into account, though. The generalisability of the findings is limited by the small sample size. The descriptive nature of the study made it difficult to prove a link between the development of AVN, rejection episodes and steroid exposure. Furthermore, using hospital-based records could have led to selection bias since subclinical instances might have been underreported, whereas more severe symptoms may have been recorded in detail.[8]

Renal transplant recipients are reported to experience AVN, a side-effect that is purportedly linked to high-dose corticosteroid regimens.[9] However, the fact that AVN occurs even in individuals receiving low-dose steroid maintenance is consistent with findings from certain case reports, indicating that steroid reduction techniques do not completely eliminate the risk.[10] Consistent with the current findings, previous studies have documented AVN incidence rates in renal transplant groups ranging from 3% to 15%, with femoral head involvement being the most common site.[3,11] The fact that 26.7% of the current cases required surgical intervention is also consistent with previous research showing that a small percentage of patients develop advanced-stage AVN that necessitates operative therapy.[12]

That 53.3% of the current patients had a recent rejection episode raises the possibility of additional steroid pulses or intensified immunosuppression as a precipitating factor for AVN, a relationship reported in previous studies.[13,14]

However, earlier research has also suggested that rejection episodes and increased steroid use are associated with a higher risk of AVN progression and surgical intervention.[15] In spite of this, the current finding of no significant association aligns with more recent reports indicating that modern low-dose steroid regimens and revised immunosuppressive protocols may reduce this risk. This implies that other variables, such as vascular reactions, non-steroidal immunosuppressants, or pre-existing bone health, may be more important in

determining surgical results in AVN.

Additionally, the fact that 93.3% of the current cases relied on MRI as the main diagnostic method highlights the increasing preference for early, sensitive imaging technologies over traditional X-rays in the detection of AVN in transplant populations.[5,16]

Other risk variables, including acute rejection events, cumulative steroid exposure, and metabolic abnormalities, may be crucial in explaining why AVN persists even after low-dose steroid regimens.[17] Even when steroid use is decreased, transplant physicians should continue to have a high suspicion of AVN when joint discomfort is prevalent in transplant recipients. Early MRI screening can help with prompt diagnosis and treatment, which may slow down the course of the disease, and enhance patient outcomes.[18]

The temporal link involving AVN onset, steroid pulses and rejection events has to be investigated in future research with bigger sample sizes and prospective approaches.[13] Studying the function of bone turnover indicators and non-steroidal immunosuppressive drugs may provide more light on the aetiology of AVN in this population.[19] Furthermore, assessing how well ultra-low dose or steroid-free immunosuppressive regimes lower the incidence of AVN may help guide future transplant procedures.[20]

Conclusion

All AVN cases involved the hip, and were primarily diagnosed by MRI, with many requiring surgery. Frequent recent rejection episodes suggest a possible link among steroid pulses, immune activation and AVN onset, though no clear cause could be identified. The importance of early imaging, ongoing monitoring of musculoskeletal symptoms, and careful management of immunosuppression must be acknowledged to minimise steroid use while preserving graft function.

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