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# Musculoskeletal manifestation of kidney transplant recipients

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## ABSTRACT

**Introduction:** Kidney transplantation has been established as an effective treatment method for patients with end-stage renal disease.**Objectives:** The purpose of this study was to determine the prevalence of musculoskeletal complaints following kidney transplant.**Patient and Methods:** We designed a retrospective-descriptive study on kidney transplant recipients. This study was performed on medical records of 1189 kidney transplant patients referring to the kidney transplantation ward of Golestan hospital (Ahvaz, Iran).**Results:** The mean age of the participants was  $42.8 \pm 13.5$  years. Out of the 1189 patients, 231 (22.3%) had musculoskeletal manifestations, with the most prevalent problem being non-inflammatory pain (41.4%). Additionally, degenerative joint disease, especially in the lumbar spine, was the most common clinical finding in this study (24%). Besides, hypovitaminose D (71.4%) and elevated parathyroid hormone levels (51.3%) and hyperuricemia (50.8%) were the most common laboratory abnormalities observed in our patients.**Conclusion:** Approximately 22.3% of our renal transplant patients had musculoskeletal manifestations. Attention to earlier detection of these manifestations through regular examinations would reduce the complications and burden of the disease.

### Implication for health policy/practice/research/medical education:

In a retrospective-descriptive study on 1189 kidney transplant patients (mean age was  $42.8 \pm 13.5$  years), we found 231 (22.3%) of cases had musculoskeletal manifestations, with the most prevalent problem being non-inflammatory pain (41.4%). Our study showed, musculoskeletal problems are common after kidney transplantation.**Please cite this paper as:** Mowla K, Shahbazian H, Sharif Najafi A, Ghorbani A. Musculoskeletal manifestation of kidney transplant recipients. J Renal Inj Prev. 2021; 10(x): x-x. doi: 10.34172/jrip.2021.xx.

## Introduction

Renal transplantation has been accepted as an effective treatment method for patients with final-stage renal disease (1). Although renal transplantation improves the physical performance of patients, it can bring about various problems since early complications after or during renal transplantation is led to countless problems in post-transplant period.

One of the complications of renal transplantation which has received less scholarly attention is musculoskeletal sequels (2), since preexisting musculoskeletal affection is intensified by immunosuppressive drugs. Musculoskeletal sequels, myopathy, joint tenderness and pain, gout,

decreased bone mass and many other complaints are among the most commonly mentioned complaints.

Additionally, these side effects are likely to occur in this population due to prolonged inactivity, widespread use of immunosuppressive drugs, diminished bone mass, kidney failure, secondary or tertiary hyperparathyroidism, and many other known and unknown factors (3-5).

## Objectives

The aim of this study was to determine the frequency of musculoskeletal involvement in kidney transplant patients.

## Patients and Methods

### Study design

We designed a retrospective descriptive study to evaluate musculoskeletal problems after renal transplantation. The investigation was carried out at the kidney transplantation unit of Golestan hospital from March 20, 2016 to March 20, 2019 on 1499 kidney transplanted patients (Ahvaz, Iran).

The patients with a past history of rheumatic disease as a primary cause of end-stage renal disease and those with transplantation history under 30 days were excluded from the study (310 patients). Therefore, the study was conducted on 1189 patients.

We assessed drug protocols, post-transplantation period (month), underlying diseases, gender, age, musculoskeletal complaints, and laboratory findings. Bone-mineral densitometry (BMD) results were obtained from the medical records of hospital archives.

The BMD was conducted by a single device, and BMDs of L1–L4 vertebrae and femur (total and neck), were measured. Values equal or less than 2.5 and values between 1 and 2.5 were considered as osteoporosis and osteopenia, respectively. Accordingly, biochemical assessments were carried out in Golestan hospital's laboratory.

### Ethical issues

The study was in accordance with the Declaration of Helsinki and its later amendments. The protocol was confirmed by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS. REC.1398.375). Accordingly, informed consent was obtained from all patients. This study was extracted from the rheumatology fellowship thesis of Asghar Sharif Najafiat this university (# U98093).

### Statistical analysis

The data of 1189 kidney transplant recipients were analyzed using SPSS (version 22.0). The assay was performed using independent sample *t* test, Mann-Whitney U, chi-square and Spearman's tests. The results were considered statistically significant for *P* values less than 0.05.

## Results

The analysis involved 1189 patients receiving renal transplantation, including 786 (66.1%) males and 403 (33.9%) females. The average age of participants was  $42.8 \pm 13.5$  years ranging from 14 to 79 years.

The mean post-transplantation period was  $67.8 \pm 67.9$  months. Additionally, the interval between transplants and hospital admissions varied from one month to 21 years (Table 1).

All patients received calcineurin inhibitor (including cyclosporine or tacrolimus) or sirolimus/mycophenolate and prednisolone in mild to moderate doses (5 to 10 mg/d). Serum calcium level (after correction based on

blood albumin) was  $8.9 \pm 0.93$  (3.7 to 12.2 mg / dL) (Table 2). Calcium levels were normal in 74.1% of patients, lower than normal in 23.6%, and higher than normal in 2.3% of the patients. Calcium disorders were more common in women than men (Table 3).

Serum intact parathyroid hormone (PTH) levels were observed in 80 patients (6.7%), ranging from 9 to 1633 pg/mL (mean  $145 \pm 214$  pg/mL) (Table 2). It was normal in 35 patients (43.8%), lower than normal in 4 patients (5%), and above normal in 41 people (51.2%) (Table 4). Serum intact PTH disorders were observed in 75%, with men (34 people) outnumbering women. Hyperparathyroidism was present in 9.4% of our patients (Table 5). Most of the cases were due to parathyroid adenoma.

Serum vitamin D levels were assessed in 91 patients (7.6%), and they were between 3.1 and 95.7 ng/cc ( $25.3 \pm 16$ ) (Table 2). Twenty-six patients (28.6%) had normal serum levels and 65 patients (71.4%) had lower than normal serum levels. Also, hypovitaminosis D was 75% in women and 71.1% in men (Table 6). In this study, the majority of laboratory disorders of vitamin D3 and PTH were observed in the age groups of 30 to 50 years (Table 7).

Uric acid levels were high in 50.8% of the patients and averaged  $7.9 \pm 2.6$  mg/dL (4–14.9) (Table 2). About a quarter of patients had crystallopathy, while gouty arthritis was more common than other crystal-induced arthropathies (Figure 1).

Since bone densitometry results were available for 0.84% of the patients, they are not interpretable. Our

**Table 1.** Demographic variables of kidney transplant recipients

<b>Patients</b>	1189
<b>Age</b>	$42.8 \pm 13.5$ (14-79 years)
<b>Male/female</b>	786 (66.1%)/403 (33.9%)
<b>Post-transplantation period (month)</b>	$67.8 \pm 67.9$ (1-252 months)

**Table 2.** Serum laboratory measurements among kidney recipients

<b>Calcium (mg/dL)</b>	$8.9 \pm 0.93$ (3.7–12.2)
<b>Phosphorus (mg/dL)</b>	$3.7 \pm 1.14$ (1–8.8)
<b>Albumin (g/dL)</b>	$4.1 \pm 0.58$ (3.3–6.3)
<b>Vitamin D (ng/mL)</b>	$25.3 \pm 16$ (3.1–95.7)
<b>iPTH (pg/ml)</b>	$145 \pm 214$ (9–1633)
<b>Uric Acid (mg/dL)</b>	$7.9 \pm 2.6$ (4–14.9)

iPTH, Intact parathyroid hormone.

**Table 3.** Percentage of serum calcium levels in men and women

Gender	Ca		
	Normal	Low	High
Male	76.3%	22.1%	1.6%
Female	69.6%	26.7%	3.7%

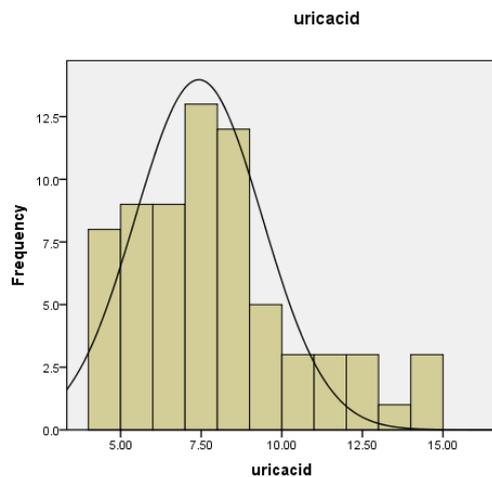


Figure 1. Serum uric acid levels in kidney transplant patients.

study showed that out of the 1189 patients, 64 (5.6%) had musculoskeletal problems, while the most prevalent affection was non-inflammatory pain (n=26, 41.4 %).

Table 4. Serum intact PTH (iPTH) levels in male and female patients

Gender	iPTH		
	Normal	Low	High
Male	45.2%	4.8%	50%
Female	38.8%	5.6%	55.6%

iPTH, Intact parathyroid hormone.

Table 5. Musculoskeletal disorders among kidney transplant recipients

Hyperparathyroidism	6 (9.4%)
Myopathy	4 (6.25%)
Neuropathy	2 (3%)
Crystallopathy	12 (18.8%)
Fracture	3 (4.7%)
Non-inflammatory (mechanical)pain	26 (41.4%)
Avascular necrosis	1 (1.5%)

Table 6. Serum vitamin D levels in men and women in kidney transplant recipients

Gender	Vitamin D		
	Normal	Low	High
Male	29.9%	70.1%	0%
Female	25%	75%	0%

Table 7. The prevalence of vitamin D and PTH abnormalities in different age groups of patients

Age groups (y)	High PTH	Low vitamin D
1-20	4.8%	1%
21-30	14.6%	9%
31-40	17.2%	19%
41-50	34.2%	17%
51-60	17%	13%
>60	12.2%	6%

Crystallopathy was observed in 18.8% (n=12) of the patients who often had gout, while the most common involved joints were the foot, ankle, wrist and knee joints. Myopathy was observed in 6.4% (n=4) of the cases. Around 4.7% of the patients experienced bone fracture (hip, rib and metatarsus). Additionally, 3% (n=2) of the patients were diagnosed with neuropathy. Avascular necrosis was seen in 1.5% (n=1) of patients. The knee joint was involved in this patient (Table 5).

## Discussion

In today's world, due to the improvement of health indicators, an increase in life expectancy of kidney transplant patients can be observed. However, our knowledge of the prevalence of musculoskeletal and rheumatological disorders in this group of patients is low. These side effects lead to sleep disorders, depression, limited activity, decreased participation in social activities, and fatigue, and represent an increasing economic and societal burden in the context of this population.

The impact of these complications is influenced and exacerbated in association with underlying diseases such as diabetes and congestive heart failure, bringing about a significant deterioration in quality of life. Musculoskeletal complaints have a considerable impact on the use of primary and specialist health services. Bone mineral disease is common in renal transplant patients, where secondary hyperparathyroidism and post-transplantation bone disease are potential effectors of both graft and vascular damage.

Additional attention needs to be paid to this group of patients; therefore they may benefit from better targeted preventive measures. Since early detection of these problems is one of the most important priorities of treatment, in this study, we assessed the prevalence of musculoskeletal disorders among kidney transplant recipients.

We found that 231 out of 1189 patients (22.3%) had musculoskeletal manifestations (complaints in 5.4% and laboratory abnormalities in 16.9%). The most prevalent chief complaint was joint pain. Our study showed that non-inflammatory pain was the most prevalent clinical finding (41.4%), with osteoarthritis of the lumbar spine and its complications (55%) being the most common.

Furthermore, hypovitaminose D was detected in 71.4% of the subjects, while higher than normal PTH levels were seen in 51.3% of the participants. Accordingly, hyperuricemia was the third common laboratory disorder in our research which was observed in 50.8% of our patients.

In the study by Sperschneider and Stein, 19-35% of the kidney transplant patients had musculoskeletal problems (7), which is almost similar to our study results. Accordingly, Diep et al found that joint and muscle pain was the most prevalent finding in their study. They

postulated that joint pain is probably due to degenerative joint disease (osteoarthritis) and peripheral neuron damage (8). Diep et al also reported that low level vitamin D was the most common biochemical abnormality in their study, which is consistent with the results of our study (8).

According to the study by Rao et al, 37% of kidney transplant recipients had musculoskeletal problems. Their observations suggest that renal transplant recipients experience significant morbidity and mortality even in the second decade (9). However, unlike our results showing that 22% of the kidney transplant patients had musculoskeletal complaints, Unterman et al found that digestive tract manifestations are prevalent problems following kidney transplantation, while musculoskeletal complaints are rare (6). This discrepancy may be due to the difference between study populations. In another study by Cianciolo et al, the prevalence of low levels of 25(OH) vitamin D<sub>3</sub> in kidney transplant patients was reported to be high, which has a direct role in the occurrence of bone disease and musculoskeletal disorders in this group of patients (10). Lee et al and Park et al demonstrated that 61.5% and 82.3% of patients had low levels of vitamin D, respectively (11,12), since the former showed a relatively higher prevalence of hypovitaminose D in females (11), which is in agreement with our study.

In the study of Bouquegneau et al, only 30% of the patients had low-levels of vitamin D (13). However, the rate of hypovitaminose D in our study was nearly twice as high as that presented by Bouquegneau et al. This finding may be related to the high frequency of hypovitaminose D in our region compared to the general population in the study by Bouquegneau et al.

PTH levels were 51.3% higher than normal in our study, while they were 63.2% and 67% higher than normal in the studies by Monier-Faugere et al and Mitterbauer et al, respectively (14-15). Likewise, Wolf et al and Akaberi et al reported that over 83%, and 40% of patients had PTH levels higher than normal, respectively (16,17).

In our study, no relationship between hypocalcemia and high PTH levels was seen ( $P=0.726$ ). Hyperparathyroidism was present in 9.4% of the patients in our study due to parathyroid adenoma. In the study of Monier-Faugere et al, the prevalence of avascular necrosis was 12.2% (14). In the study of Vogel et al, the most commonly involved sites were the hip, knee and shoulder joints (18). Meanwhile, Nel and Epstein reported that avascular necrosis prevalence was up to 41% of their patients (5). In our study, this rate was 1.5%, which is significantly less frequent. We postulate that the difference in the method and the extension of evaluation of avascular necrosis could explain the different results. In our study, only the knee was involved. Cumulative corticosteroid dose of more than 2 g and persistent hyperparathyroidism could increase the avascular necrosis chances (3).

In our research, high uric acid was found in 50.8% of the patients while only 25% had crystallopathy. The

relationship between crystallopathy and high levels of uric acid was statistically significant ( $P<0.001$ ), while the correlation of high levels of uric acid with post-transplantation period ( $P=0.918$ ) and age groups ( $P=0.962$ ) was not significant. In our study no relationship between post-transplantation period and elevated uric acid levels was detected ( $P=0.99$ ), however, in the study by Sullivan et al, this rate was reported to be 28% (19).

Consistent with our study, Stamp et al estimated the prevalence of gout to be 23% (20). Brigham et al, on the other hand, showed that 8% of their patients had gout. These patients were more prone to uncontrolled gout attacks, tophi, and failure of response to allopurinol (21). In the study by Simbolon et al, the prevalence of gout in the first three years after transplantation was reported to be 8.8% (22).

In our study, crystallopathy was observed in 18.8% of the patients, of whom 83% probably had gout. Additionally, myopathy was present in 6.3% of the patients due to some drugs such as colchicine and corticosteroid.

Chan et al found that low-muscle strength is common among kidney transplant patients, conferring poor prognosis in the medium term (23). Ozkayar et al showed that low-muscle strength (sarcopenia), may develop at an earlier age in kidney transplant recipients. There was a statistically significant positive correlation between vitamin D levels and handgrip strength (24). Additionally, the prevalence of muscle disorders was 17.9% in the study of Attallah et al (25).

## Conclusion

We showed that musculoskeletal problems are common after kidney transplantation. Awareness of the relation between kidney transplant and musculoskeletal disorders may help to focus on the wide range of diagnoses that could be otherwise overlooked.

## Limitations of the study

One major limitation in this study is that we did not have access to sufficient medical record data including data about the patients' bone mineral densitometry, and this is because either the patients failed to provide the data, or they might have referred to other healthcare facilities. More studies, however, have to be conducted to determine the effective factors contributing to the occurrence of musculoskeletal disorders.

## Authors' contribution

ASN, KM, HS, and AG were involved in the conception of the study. ASN participated in data collection and analysis and drafted the manuscript. AG and ASN contributed to drafting, detailed review, and completion of the manuscript. All authors were involved in preparing this manuscript both in drafting the manuscript and approving the final draft.

### Conflicts of interest

The authors declare that there is no conflict of interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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