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Musculoskeletal disorders in hemodialysis patients: prevalence, clinical symptoms, and associated factors

Hanie Ranaei[1], Vajehallah Raeesi[2], Fatemeh Salmani[3], Soroush Khojasteh-Kaffash[1], Zeinab Saremi[2,4*]

[1]Student Research Committee, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[2]Department of Internal Medicine, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[3]Department of Epidemiology and Biostatistics, School of Health, Birjand University of Medical Sciences, Birjand, Iran
[4]Clinical Research and Development Unit, Valiasr Hospital, Birjand University of Medical Sciences, Birjand, Iran

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ABSTRACT

Introduction: One of the major public health problems is end-stage renal disease (ESRD). ESRD is commonly associated with musculoskeletal disorders (MSDs).

Objectives: Due to the importance of MSDs in hemodialysis patients and the absence of sufficient studies in Iran, this study aims to investigate MSDs in hemodialysis patients.

Patients and Methods: This cross-sectional study was conducted on 75 patients with ESRD, who were under hemodialysis at the special diseases center of Birjand university of medical sciences, south Khorasan, Iran. Inclusion criteria were history of at least 2 years of hemodialysis, and age more than 18 years. All patients with previous neurological disorders, previous rheumatic diseases, previous arthroplasty of the limbs, and severe psychological disorders were excluded from the study. Baseline characteristics and laboratory data collected. MSDs examined based on the Nordic Musculoskeletal Screening Questionnaire (NMQ). Data were described using central tendency, CHI-SQUARE test, and Fisher's exact test were used. The significance level in this study was $P<0.05$.

Results: Seventy-five patients participated (Mean and standard deviation (SD) of age: 62.13±1.73 years, male to female ratio: 1.14). Sixty-three patients (84.0%) had MSDs. There was no significant difference based on age, dialysis vintage, gender, laboratory tests, and comorbidities ($P>0.05$). Dialysis etiology, knee osteoarthritis, shins pain, knee pain and knee range of motion had significantly difference between groups (respectively, $P=0.047$, $P=0.003$, $P=0.012$, $P=0.001$, $P=0.002$).

Conclusion: The frequency of MSDs in these patients was 84.0%. There was a significant association between MSDs with the cause of hemodialysis, lower limb pain, and knee osteoarthritis.

Implication for health policy/practice/research/medical education:
The number of patients needing hemodialysis is increasing worldwide. Considering the high prevalence of musculoskeletal disorders in these patients and its impact on the patients' quality of life, it is important to determine the incidence, prevalence and factors affecting its development and severity.

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Introduction

End-stage renal disease (ESRD) is a major public health problem. In the United States, 350 000 patients with ESRD are being treated with dialysis, of which 92% are hemodialysis and 8% are undergoing continuous ambulatory peritoneal dialysis (1). Musculoskeletal disorders (MSDs) are damage or dysfunction in nerves, muscles, cartilages, tendons, ligaments, joints and spinal discs (2). Chronic kidney disease (CKD) and ESRD are commonly associated with MSDs, which are called chronic kidney disease-mineral and bone disorder (CKD-MBD). According to the International Society of Nephrology's (ISN) 2019 Global Kidney Health Atlas (GKHA) cross-sectional survey of 160 countries, the incidence of ESRD worldwide was 144 individuals per million general population (3). Pain is known as one of the most important problems in medical care, and half of hemodialysis patients suffer from chronic pain,

***Corresponding author**: Zeinab Saremi, Email: zsaremi@bums.ac.ir

which is usually not properly managed (4). Biochemical disorders of calcium and phosphorus metabolism caused by CKD and hemodialysis can cause a wide variety of bone and soft tissue abnormalities. These abnormalities, known as renal osteodystrophy, appear clinically in the form of secondary hyperparathyroidism, osteomalacia, rickets, adynamic bone, and soft tissue calcification. In addition, long-term hemodialysis can be associated with amyloid deposition, destructive spondyloarthropathy, osteonecrosis, and musculoskeletal infections (5). MSDs are one of the important factors in reducing the quality of life of kidney failure patients, especially patients with long-term hemodialysis (6,7). The term renal osteodystrophy was conducted for the first time in 1943 and refers to the set of MSDs in patients with CKD (8). Hemodialysis was also proposed for the first time in the 1960s, and after a short time, its muscular and skeletal complications were identified. A pervious study reported that out of every six patients who underwent hemodialysis, five of them suffered from periarthritis and arthritis (9). Over the years, rheumatological problems related to the deposition of apatite crystals were increased. Due to more effective treatments of hyperphosphatemia, inflammatory mediators in the joints decreased. Moreover, carpal tunnel syndrome was reported as one of the hemodialysis complications, and amyloidosis was found as a one of the common causes of MSDs (10). In the early 1980s, chronic arthropathies of hemodialysis patients were interpreted. In the following years, it was defined that arthropathies were the result of amyloidosis. Beta 2-myglobulin was diagnosed in amyloidosis as a result of chronic hemodialysis (11). In 2005, the Kidney Disease Organization proposed new terms that include a wide range of clinical syndromes with CKD, and disorders related to bone and mineral metabolism (12).

Objectives

Considering the importance of MSDs in hemodialysis patients and the lack of sufficient studies in Iran, this study aims to investigate MSDs in hemodialysis patients, determine the prevalence and frequency of MSDs, and associated conditions.

Patients and Methods

Study design

This cross-sectional study was conducted on all patients with ESRD, who hemodialysis at the Special Diseases Center of Birjand University of Medical Sciences, south Khorasan, Iran. In this study, inclusion criteria were history of at least two years of hemodialysis, and age more than 18 years. All patients with previous neurological disorders, previous rheumatic diseases, previous arthroplasty of the limbs, and severe psychological disorders were excluded from the study. Finally, out of 124 patients of this center, 77 patients were selected to participate in this study, and due to the death of 2 patients during the study, 75 patients were included in the final analysis. After explaining the purpose and upcoming processes, written informed consent was obtained from all patients to participate in the study. Baseline characteristics including demographic information, dialysis vintage, history of hypertension (HTN), diabetes, dyslipidemia, heart diseases, psychiatric disorders, calcium and vitamin D supplements consumption, daily activity, number of sessions/weeks of dialysis, and history Previous musculoskeletal diseases were collected. Laboratory tests include complete blood cell count (CBC), phosphorus (P), calcium (Ca), uric acid, creatinine (Cr), aspartate transaminase (AST), parathormone (PTH), ferritin, albumin, alanine transaminase (ALT), Iron (Fe), total protein, alkaline phosphatase (ALP), total iron binding capacity (TIBC), and blood urea nitrogen (BUN) were conducted. Musculoskeletal examination was performed by a rheumatologist and a senior resident of internal medicine. Musculoskeletal pain examined based on the Nordic Musculoskeletal Screening Questionnaire (NMQ) (13). The severity of the MSDs was assessed by the patients based on a pain rating scale out of 10.

Statistical analysis

All data, including demographic information and clinical and paraclinical findings, were entered into the statistical software IBM SPSS Statistics for Windows, version 19 (IBM Corp., Armonk, N.Y., USA). Data were described using central tendency and dispersion indices, quantitative data in the form of mean and standard deviation, and qualitative data in the form of frequency and frequency percentage. After checking the normality of quantitative data using the Kolmogorov-Smirnov test, suitable non-parametric tests were used. Chi-square test and Fisher's exact test if required, was employed to analyze qualitative data and Mann-Whitney U test was used to compare quantitative data between two groups. The significance level in this study was $P<0.05$.

Results

In this cross-sectional study, 75 hemodialysis patients participated (mean and standard deviation (SD) of age: 62.13 ± 1.73 years, male to female ratio: 1.14). Based on physical examination and NMQ questionnaire, 63 patients (84.0%) had MSDs. None of the participants in this study had gout. According to Table 1, the mean age in patients with MSDs was higher than other patients, however there was no statistically significant difference among them (62.63 versus 59.50, $P=0.402$). There was no significant difference in the male to female ratio between groups which present in this study ($P=0.377$). Body mass index (BMI) in patients with MSDs was lower than other patients (22.76 versus 25.39, $P=0.214$). The dialysis vintage was higher in patients with MSDs, although it was not statistically significant (5.60 years versus 4.58 years,

Table 1. Baseline characteristics of patients according to the presence of musculoskeletal symptoms (N=75)

	All patients	Patients without MSDs	Patients with MSDs	*P* value
N	75	12	63	
Age (years) (SD)	62.13 (1.73)	59.50 (15.87)	62.63 (14.90)	0.402[a]
Dialysis duration (y) (SD)	5.44 (3.05)	4.58 (3.44)	5.60 (2.98)	0.570[a]
BMI (kg/m^2) (SD)	23.18 (0.62)	25.39 (6.32)	22.76 (5.11)	0.214[a]
Gender ratio (M/F)	40/35	5/7	35/28	0.377[b]
Job				
Employed (%)	6 (8.0)	1 (8.3)	5 (7.9)	0.963[b]
Disable (%)	69 (92.0)	11 (91.7)	58 (92.1)	
HTN (%)	50 (66.7)	10 (83.3)	40 (63.5)	0.181[b]
Diabetes mellitus (%)	29 (38.7)	3 (25.0)	26 (41.3)	0.289[b]
Hyperlipidemia (%)	32 (42.7)	5 (41.7)	27 (42.9)	0.939[b]
Cardiovascular disease (%)	24 (32.0)	3 (25.0)	21 (33.3)	0.571[b]
Vitamin D and calcium supplements usage (%)	74 (98.7)	12 (100.0)	62 (98.4)	0.660[b]
Etiology of dialysis				
Diabetes mellitus (%)	9 (12.0)	0 (0.0)	9 (14.3)	**0.047[b]**
HTN (%)	28 (37.3)	9 (75.0)	19 (30.2)	
HTN with Diabetes mellitus (%)	28 (37.3)	3 (25.0)	25 (39.7)	
Congenital (%)	9 (12.0)	0 (0.0)	9 (14.3)	
Others (%)	1 (1.3)	0 (0.0)	1 (1.6)	
History of organ transplant (%)	7 (9.3)	1 (8.3)	6 (9.5)	0.897[b]
Number of sessions/weeks				
2 Sessions/week (%)	3 (4.0)	1 (8.3)	2 (3.2)	0.403[b]
3 Sessions/week (%)	72 (96.0)	11 (91.7)	61 (96.8)	
Cinacalcet usage (%)	4 (5.3)	1 (8.3)	3 (4.8)	0.614[b]
Previous MSD (%)	24 (32.0)	1 (8.3)	23 (36.5)	0.055[b]
Musculoskeletal disorder severity				
Without MSD (%)	18 (24.0)	7 (58.3)	11 (17.5)	**0.024[b]**
Mild (%)	27 (36.0)	3 (25.0)	24 (38.1)	
Moderate (%)	18 (24.0)	1 (8.3)	17 (27.0)	
Severe (%)	12 (16.0)	1 (8.3)	11 (17.5)	
Previous psychosis (%)	7 (9.3)	0 (0.0)	7 (11.1)	0.225[b]
Musculoskeletal signs and symptoms				
Knee osteoarthritis (%)	29 (38.7)	0 (0.0)	29 (46.0)	**0.003[b]**
Morning stiffness (%)	1 (1.3)	0 (0.0)	1 (1.6)	0.660[b]
Low back pain (%)	11 (14.7)	0 (0.0)	11 (17.5)	0.117[b]
Shins pain (%)	23 (30.7)	0 (0.0)	23 (36.5)	**0.012[b]**
Knee pain (%)	32 (42.7)	0 (0.0)	32 (50.8)	**0.001[b]**
Gower sign (%)	10 (13.3)	0 (0.0)	10 (15.9)	0.138[b]
Decreased knee range of motion (%)	30 (40.0)	0 (0.0)	30 (47.6)	**0.002[b]**
Laboratory tests				
Hemoglobin, g/dL (SD)	11.71 (0.11)	11.92 (1.12)	11.67 (0.93)	0.385[a]
PLT, ×10^3/µL (SD)	253.66 (13.33)	261.66 (93.76)	252.14 (119.79)	0.670[a]
Ca, mmol/dL (SD)	8.47 (0.08)	8.62 (0.81)	8.44 (0.67)	0.438[a]
P, mmol/dL (SD)	5.47 (0.13)	5.59 (1.37)	5.45 (1.16)	0.828[a]
Uric acid, mg/dL (SD)	5.89 (0.14)	6.21 (1.34)	5.82 (1.26)	0.259[a]
PTH, pg/dL (SD)	437.14 (30.29)	489.16 (334.51)	427.23 (248.31)	0.745[a]

Table 1. Continued

	All patients	Patients without MSDs	Patients with MSDs	*P* value
BUN, mg/dL (SD)	100.80 (3.86)	102.83 (36.70)	100.41 (33.10)	0.845[a]
TIBC (SD)	229.12 (5.48)	214.83 (46.10)	231.84 (47.65)	0.406[a]
ALP, UI/dL (SD)	316.96 (17.77)	316.83 (147.78)	316.98 (156.20)	0.897[a]
AST, UI/dL (SD)	19.74 (1.01)	19.91 (9.32)	19.71 (8.80)	0.669[a]
ALT, UI/dL (SD)	21.77 (1.23)	20.0 (9.94)	22.11 (10.91)	0.231[a]
Albumin, g/L (SD)	3.80 (0.05)	3.67 (0.48)	3.82 (0.49)	0.477[a]
Ferritin, µg/L (SD)	221.98 (20.90)	214.91 (262.87)	223.33 (163.81)	0.225[a]
Cr, mg/dL (SD)	6.96 (0.22)	7.87 (2.44)	6.78 (1.78)	0.185[a]
Vitamin D, UI/dL (SD)	39.50 (2.49)	38.66 (26.38)	39.66 (20.82)	0.563[a]
Fe, µg/dL (SD)	81.52 (5.95)	93.75 (76.54)	79.19 (45.82	0.925[a]

MSDs, Musculoskeletal disorders; BMI, Body mass index; HTN, Hypertension; PTH, Parathormone hormone; PLT, Platelets; Ca, Calcium; P, Phosphorous; BUN, Blood urea nitrogen; TIBC, Total iron binding capacity; ALP, Alkaline phosphatase; AST, Aspartate transaminase; ALT, Alanine transaminase; Cr, Creatinine; Fe, Iron.

[a] Mann-Whitney U test.

[b] Chi-square test and Fisher's exact test.

Statistical significant difference (*P* value <0.05) are bolded.

P=0.570). The most common comorbidity in both groups with and without MSDs was HTN (63.5% versus 83.3%, respectively). The frequency of comorbidities was not significantly different between the two groups (P>0.05). The most common cause of dialysis in patients with MSDs was HTN with diabetes (39.7%), since in patients without MSDs was HTN (75.0%). Thus, a significant difference was observed between the two groups based on the etiology of ESRD and hemodialysis ($P=0.047$). There was no significant difference in history of previous MSDs between the two groups. Among the musculoskeletal signs and symptoms, the frequency of pain, osteoarthritis and decreased range of motion in knee joint were significantly higher in the MSDs group ($P=0.001$, $P=0.003$ and $P=0.002$, respectively). There was only one patient (1.3%) with carpal tunnel syndrome in all patients. The most common clinical finding in all patients was knee pain (42.7%). Shin splints was also significantly higher in patients with MSDs (36.5% versus 0.0%, $P=0.012$). There was no significant difference between the two groups based on all laboratory tests ($P<0.05$).

Discussion

This study was conducted with the aim of investigating MSDs in hemodialysis patients, determine the prevalence and frequency of MSDs and associated conditions in patients with a history of more than two years of dialysis. This cross-sectional study was conducted on 75 hemodialysis patients at the special diseases center of Birjand university of medical sciences, south Khorasan, Iran. The frequency of MSDs was 84.0%, which is higher than previous studies (49.0%-78.0%) (14-19). This difference in the frequency of MSDs can be due to the older age of the patients in the present study, and the difference in diagnostic criteria of MSDs. The patients who present in this study were ESRD and all of them were undergoing hemodialysis, while in some of other studies, patients in stages 3 to 5 of CKD investigated.

The most common musculoskeletal clinical finding was knee pain (42.7%). Pain was observed as one of the most common clinical findings in previous studies (41.0%-50.0%) (4,17). Due to the lower dialysis vintage compared to previous studies and due to the direct association between MSDs and dialysis vintage, it is expected that in the coming years the frequency of MSDs and its symptoms, including pain, increases. Based on previous studies, pain in hemodialysis patients occurs mostly in the form of headache and pain in the lower limbs, which is consist with the present study (2). Many patients complained of disability and reduced performance and daily activities, which according to a systematic review study, acute and chronic pain in hemodialysis patients is associated with disability and dysfunction (20).

Dialysis vintage was not significantly related to the occurrence MSDs, which was inconsistent with previous studies (15,18). This difference can be explained by the short duration of hemodialysis in these patients compared to the patients in other studies. Based on previous studies, skeletal-muscular symptoms are expected to appear around the 7th year of hemodialysis (15,16,19). This cut point is 1.56 years more than the mean of dialysis vintage in present study.

The third most common clinical finding in this study was osteoarthritis of the knee (38.7%) and its frequency was lower than previous studies (18). Considering the direct association between osteoarthritis with age and race, this difference can be due to the younger age and different race of the patients compared to other studies (21). The higher frequency of osteoarthritis compared to its frequency in the general population at the same age (13.9%) can be due

to renal osteodystrophy and mineral and bone disorders (MBD) (21). The main causes of renal osteodystrophy in CKD and hemodialysis patients include phosphorus retention, impaired vitamin D metabolism, chronic metabolic acidosis, secondary hyperparathyroidism, and increased fibroblast growth factor 23 (FGF23) (22).

In the present study, there was no significant difference in the serum levels of phosphorus, alkaline phosphatase and parathyroid hormone (PTH) between the two groups. The serum levels of phosphorus, alkaline phosphatase and PTH are known as risk factors for mortality in CKD patients (23). The study by Wang et al, showed that low and high PTH serum levels in hemodialysis patients with residual renal clearance of less and more than 1.5 mL/min/1.73 m^2 increased mortality, respectively (23). Therefore, regulating PTH level, according to the remaining renal clearance of patients, is recommended as an important factor in the development of renal osteodystrophy and mortality in CKD patients. It should be noted that in this study, patients' serum samples were taken before hemodialysis. A previous study demonstrated that high and low levels of phosphorus and low levels of PTH were associated with impaired physical function (24).

Most of the patients in this study did not have MSDs or had mild MSDs. This finding can be justified considering the monthly examination of serum levels of factors related to bone mineralization and the prescription of vitamin D3 and calcium supplements for patients. The average serum levels of phosphorus, calcium and vitamin D3 in the present study are in the safe range for renal osteodystrophy (14). However, the serum PTH concentration is higher than the safe limit (>100 pg/mL) and reducing its level is recommended to prevent MSDs and its progression (14).

Conclusion

Based on our best knowledge, this study is one of the first studies aimed at investigating MSDs in hemodialysis patients using the NMQ questionnaire, in Iran. According to the results, the frequency of MSDs in these patients was 84.0%. There was a significant association between MSDs with the cause of hemodialysis, lower limb pain, and knee osteoarthritis. No significant association was found between age, gender, dialysis vintage, and the level of serum factors with MSDs.

Limitations of the study

The lack of access to a larger sample size and conducting a multicenter study in different regions with different prevalence of MSDs is known as a limitation in the present study.

Authors' contribution

Conceptualization: Zeinab Saremi, Vajehallah Raeesi.
Data curation: Zeinab Saremi, Hanie Ranaei.
Formal analysis: Soroush Khojasteh-Kaffash, Fatemeh Salmani.
Investigation: Zeinab Saremi, Hanie Ranaei.
Methodology: Fatemeh Salmani.
Supervision: Vajehallah Raeesi, Zeinab Saremi.
Writing–original draft: Zeinab Saremi.
Writing–review & editing: Soroush Khojasteh-Kaffash, Hanie Ranaei, Zeinab Saremi, Fatemeh Salmani.

Conflicts of interest

The authors have no conflicts of interest. Authors indicate that they did not have a financial relationship with the organization that sponsored the research and had full control of all primary data and agree to allow the journal to review their data if requested.

Ethical issues

The research adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Birjand University of Medical Sciences (Ethical code# IR.BUMS.REC.1401.245). Written informed consent was obtained from all participants prior to any intervention. This study was part of Hanie Ranaei M.D.'s thesis at the university (Thesis #456793). The authors have fully adhered to ethical considerations, including plagiarism, data fabrication, and double publication.

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