Research Article

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Rheumatic and musculoskeletal manifestations in renal hemodialysis patients

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Objectives: To determine the frequency of Rheumatic and Musculoskeletal Diseases (RMDs) in patients with renal failure on regular hemodialysis. Methods and findings: The present study included forty-nine patients (28 males and 21 females) with renal failure on regular hemodialysis. Full history taking and clinical examination were documented for all patients. Blood samples were collected for laboratory investigations before the mid-week session. Dual Energy X-ray Absorptiometry (DXA) was performed to all patients to assess bone mineral density (BMD). Kt/V was used as a marker of dialysis adequacy. Mean age for all patients was 54.41 ± 15.9 years, and the dialysis duration was 3 ± 2.3 years. The detected RMDs included (in order of descending frequency): fibromyalgia syndrome (51%), myalgias (37%), arthralgia (37%), flexor tenosynovitis (29%), cramps (29%), ectopic calcifications (25%), flexion deformity of the elbow (16%), carpal tunnel syndrome (14%), destructive spondyloarthritis (8%) and Vasculitis (4.1%). Positive anti-CCP was detected in 1 female and rheumatoid factor in 4 females and 1 male. The BMD was reduced with the DXA t-score at lumbosacral spine, hip and forearm -1.5 ± 1.8, -1.7 ± 1.6, -1.9 ± 1.9 respectively. Overall, there was a tendency to a higher frequency of musculoskeletal findings in males. Other co-morbidities included: diabetes mellitus (45%), hypertension (96%), cardiovascular (33%), cerebrovascular stroke (6%), hyperuricemia (37%), hepatitis C (16%) and amyloidosis (8%). Conclusion: Rheumatic and musculoskeletal diseases are frequent and overlooked among hemodialysis patients especially males and usually associated with chronic pain.

Keywords: musculoskeletal • comorbidities • renal hemodialysis

Introduction

Pain is an important health care problem that is specifically significant among renal failure patients. It has been found that more than half of the hemodialysis patients suffer from chronic pain which is usually inadequately managed [1] Biochemical disturbances of the calcium-phosphate metabolism stimulated by chronic renal insufficiency and hemodialysis can induce wide spectrum of bone and soft tissue abnormalities. These abnormalities known as renal osteodystrophy are manifested clinically in the form of secondary hyperparathyroidism, osteomalacia/rickets, osteoporosis, adynamic bone disease and soft tissue calcification. In addition, long-term hemodialysis can be complicated by amyloid deposition, destructive spondyloarthropathy, osteonecrosis, and musculoskeletal infections [2]. Although renal osteodystrophy keeps getting great consideration, yet these musculoskeletal problems stand as one of the fundamental constraints of the quality of life of renal failure patients, especially those maintained on long-term hemodialysis [3].

As previously mentioned, long-term regular hemodialysis for chronic renal failure is associated with amyloidosis [4]. This is because hemodialysis does not sufficiently restore all aspects of normal renal function. As a result, amyloid deposition occurs in musculoskeletal structures leading to what is clinically known as dialysis-related amyloidosis. Manifestations of dialysis-related amyloidosis include a destructive arthropathy, erosive spondyloarthropathy, and bone cysts. Carpal Tunnel Syndrome (CTS) is common and, together with flexor tendon contractures and trigger finger [5,6].

Disturbed mineral metabolism is strongly associated with chronic pain in long-term hemodialysis patients [7]. Arthritis was present in 82% of patients maintained on dialysis due to end stage renal disease. Arthropathy was present in 50% due to calcium pyrophosphate dihydrate deposition disease, osteoarthritis, calcific periarthritis or elevated ferritin [8].

Pain is a common complaint of end-stage kidney disease patients, however, little is known

regarding its causes, which makes its management sometimes overlooked. The purpose of this work is to describe the incidence and determine the frequency of musculoskeletal diseases and comorbidities in patients with end-stage renal disease maintained on regular hemodialysis.

Patients and methods

This cross-sectional study, conducted at Ain Shams University hospital, included 49 patients diagnosed with renal failure and maintained on regular hemodialysis. The patients were subjected to full history taking and clinical examination. Fibromyalgia syndrome (FMS) was diagnosed according to the 2010 American college of rheumatology criteria [9]. The study has been performed in accordance with the Helsinki declaration and its revision 2013. It was, also, approved by the local ethics committee. Moreover, Patients gave informed consent to be included in the study.

Before the mid-week session, blood samples were collected for the following laboratory investigations: Hemoglobin content, serum albumin, aspartate transaminase, serum creatinine, blood urea nitrogen (pre and post dialysis), serum uric acid, serum calcium, phosphorus, parathormone (PTH), potassium, iron, ferritin and vitamin D. The Anti-Nuclear Antibody (ANA), anti-cyclic citrullinated peptide (anti-CCP) and Rheumatoid Factor (RF) were performed. The bone mineral density (BMD) was assessed by Dual energy X-ray Absorptiometry (DXA) in all patients. Plain X-ray, as well, was performed for the affected joints.

To quantify hemodialysis treatment adequacy, Kt/V was used as a marker (where: K-Dialyzer clearance of urea, t-dialysis time, V-volume of distribution of urea, approximately equal to patient's total body water). The parameters used for calculation of sKt/V (single pool) include: serum blood urea nitrogen (mg/dl) pre-dialysis and post-dialysis, Weight of the patient pre-dialysis and post-dialysis, treatment time (minute) and frequency of treatments/week. Kt/V was then calculated using the online calculator: http://www.davita.com/ktvcalculator/. The US National Kidney Foundation Kt/V target for hemodialysis is around 1.3 so that the delivered dose is at least 1.2 [10].

Statistical analysis: Data were analysed using version 21 of the statistical package SPSS. Mean and standard deviation (of quantitative variables and frequencies (number of cases) and

Table 1. Demographic and laboratory findings and comorbidities in the patients on hemodialysis.

Findings	Hemodialysis patients (n=49)	
	Mean ± SD	(median;range)/n(%)
Age (y)	54.4 ± 15.9	(53.5;12-90)
Weight (kg)	67 ± 19.5	(62.5; 27.5-126)
Dialysis Duration (y)	3 ± 2.3	(2.5; 1-11)
Kt/v	1.3 ± 0.3	(1.3; 0.6-1.9)
Laboratory findings		
Hemoglobin (g/dl)	10.7 ± 1.3	(10.9; 7.7-13.3)
C-reactive protein (mg/dl)	31.2 ± 46.3	(9; 0.9-212.3)
Albumin (mg/dl)	3.5 ± 0.4	(3.5; 2.4-4.2)
Aspartate transaminase (U/L)	18.6 ± 7.6	(18; 8-50)
Creatinine (mg/dl)	9.2 ± 3.5	(9.85; 3-18.4)
Urea Predialysis (mg/dl)	64.7 ± 17.8	(70;34-93)
Postdialysis	23.9 ± 7.9	(25;9-46)
Serum uric acid (mg/dl)	6.4 ± 2.2	(6.45; 2.4-11.5)
Parathyroid hormone (pg/dl)	588.4 ± 581.6	(358; 23-2500)
Calcium (mg/dl)	8.9 ± 0.7	(9;7.6-10.8)
Phosphorus (mg/dl)	4.9 ± 1.9	(5;2-9.9)
Potassium (mg/dl)	4.8 ± 0.7	(5;3.5-6.8)

Iron (µg/dl)	71.9 ± 29.3	(59.5; 32-154)
Ferritin (ng/ml)	689.1 ± 738.6	(437; 42-2883)
Comorbidities		
Diabetes mellitus	22 (44.9)	
Hypertension	47 (95.9)	
Hyperuricemia	18 (36.7)	
Hyperparathyroidism	29 (59.2)	
Cardiovascular	16 (32.7)	
Cerebrovascular stroke	3 (6.1)	
Hepatitis C virus	8 (16.3)	
Amyloidosis	4 (8.2)	

SD: Standard Deviation, y: years, Kg: Kilograms, mg/dL: milligrams per deciliter, µg/dl: micrograms per deciliter, ng/ml: nanogram per deciliter, Kt/v: K-Dialyzer clearance of urea, t: dialysis time, V: volume of distribution of urea.

relative frequencies (percentages)), were used for summarization of categorical data. The median and interquartile range of the numerical data is presented. Comparisons were done using the non-parametrical Mann-Whitney test. Chi square (χ^2) test was used for comparing categorical data. When the expected frequency is less than 5, Exact test was used instead. Correlations were done between quantitative variables using Spearman correlation coefficient. P-values were considered statistically significant if less than 0.05.

Results

The study included 49 patients undergoing regular hemodialysis with a mean age of 54.4 ± 15.9 years (median 53.5; range 12-90 years). They were 24 males and 18 females. Table 1 shows the Demographic and laboratory findings and comorbidities in the patients on hemodialysis. Table 2 shows the musculoskeletal findings of the patients. Osteonecrosis of the head of femur is presented in Figure 1 and brown tumor of the shoulder in Figure 2.

On comparing the findings of the patients according to the gender, the Ktv was significantly higher in females (1.39 ± 0.27) compared to males (1.14 ± 0.26) (p=0.002). There was a significantly to better reduction of the post dialysis urea in females to 21.2 ± 7.4 mg/dl) compared to the males (25.9 ± 7.8 mg/dl) (p= 0.037). HCV was positive in 8 males and none of the females. Compared to females, males had a tendency to have higher frequency of the following findings: myalgias (46.4% *vs* 23.8%), FMS (64.3% *vs* 33.3%), Arthritis (14.3% *vs* 4.8%), CTS (17.9% *vs* 9.5%), ectopic calcification (28.6% *vs* 19.05%) and amyloidosis (10.7% *vs* 4.8%). However, Osteonecrosis was found in only one male. Anti-CCP was positive in one female, whereas RF was positive in 4 females and 1 male. All other findings were comparable between males and females.

Discussion

Chronic pain due to musculoskeletal problems is common in patients with end-stage kidney disease undergoing haemodialysis [11]. Almost all hemodialysis patients have one or more musculoskeletal problems, the most common of which are muscle cramps, myalgias and arthralgias [12].

In the current study, patients' mean age was 54.4 ± 15.9 years. Comorbidities were present in the form of diabetes mellitus (44.9%), hypertension in 95.9%, cardiovascular disease in 32.7% and stroke in 6.1%. Hyperuricemia was present in 36.7% of the cases.

In another recent study, the age group was comparable 63.3 ± 14.1 years and 42.5% were males. Diabetes was present in 30.7%, hypertension in 62.7%, cardiovascular disease (CVD) manifestations in 7.6% and stroke in 4.2% [11]. Andreu-Periz et al. reported that age and the comorbidities associated with End Stage Renal Disease (ESRD) impair the functional autonomy of patients on haemodialysis. They also mentioned that in patients on hemodialysis, diabetes has been reported in 35.7%, cardiovascular disease in 29.1% and musculoskeletal alterations in 87% [12,13]. Likewise, Ashby et al. described data of 46 survivors of long term hemodialysis and found that musculoskeletal complications (78%) were among the significant morbidities that accumulate over the time on dialysis [14]. Chronic musculoskeletal pain in haemodialysis

Table 2. Musculoskeletal findings in the patients on hemodialysis

Findings	Hemodialysis patients (n=49)	
	Mean ± SD	(median;range)/n (%)
Myalgias	18	-36.7
Recurrent cramps	11	-28.6
Flexor tenosynovitis	14	-28.6
Flexion deformity Elbow	8	-16.3
Flexion deformity Knee	5	-10.2
Arthralgia	18	-36.7
Arthritis	5	-10.2
Vasculitis	2	-4.1
Osteonecrosis	2	-4.1
Ectopic calcification	12	-24.5
destructive SpA	4	-8.2
Fibromyalgia syndrome	25	-51.02
Carpal tunnel syndrome	7	-14.3
Peripheral neuritis	6	-12.2
Anti-CCP +ve	1	-2.1
Rheumatoid factor +ve	5	-10.2
Anti-nuclear antibody +ve	1	-2.1
Vitamin D (ng/ml)	25.1 ± 14.6	(20.9; 6.8-68.8)
DXA LSS	-1.5 ± 1.8	(-1.45; -5-5.7)
Hip	-1.7 ± 1.6	(-1.6; -5.3-1.2)
Forearm	-1.9 ± 1.9	(-1.8; -6.2-0.7)

SpA: Spondyloarthritis, Anti-CCP: anti-cyclic citrullinated peptide, DXA: Dual energy X-ray absorptiometry, LSS: Lumbosacral spine.

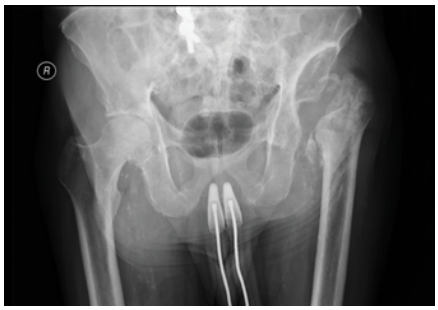

Figure 1. Osteonecrosis in the left head of femur in a patient on long term hemodialysis.

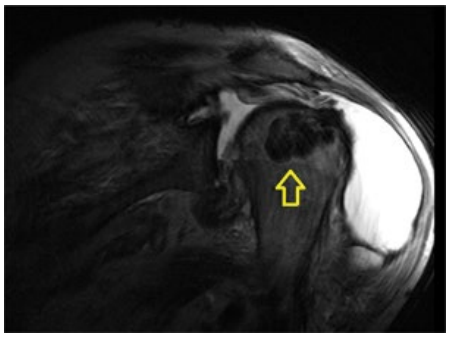

Figure 2. Large soft tissue mass in left shoulder region (brown tumor) with intra-articular portion and para-articular extension, infilteration and displacement of surrounding rotator cuff and left upper arm muscles in a patient with hyperparathroidism and renal osteodystrophy on long-term hemodialysis. Erosions of the greater tuberosity of the humerus are shown (arrow).

patients was significantly associated with hyperuricemia as co-morbidity [11]. The role of uric acid on the pathogenesis and progression of CKD is remarkable and is associated with several risk factors including diabetes, hypertension, oxidative stress and inflammation. Hyperuricemia is a common factor linking CKD and CVD [15] and is an independent risk factor for renal functional impairment [16].

There was a reduced bone mineral density and insufficient vitamin D status in the present renal hemodialysis patients. The PTH was notably increased in the hemodialysis patients (584.5 ± 614.4 pg/ml); 59.2% had hyperparathyroidism. It is worth noting that renal osteodystrophy

results from multiple contributing factors present in case of chronic renal failure. One of these factors is the uremic state itself, which can lead to inhibition of calcification. Inefficient filtration, in addition, results in phosphate retension. Both, inhibition of calcification and phosphate retension contribute to low serum calcium and osteomalacia. Acquired insensitivity to vitamin D is another factor which adds to the reduced bone mineralization. The result is stimulation of PTH secretion; hypocalcaemia with hyperphosphataemia leading to increased bone resorption and decreased bone density [17]. Hence, chronic renal failure patients should be supplied with vitamin D because it increases calcium and phosphorus absorption and decreases bone turnover [3]. Secondary hyperparathyroidism, the third factor, combined with adynamic bone disease and osteomalacia, represent the main bony problems in chronic renal failure which are responsible for a reduction in BMD [18]. Many complications can result from secondary hyperparathyroidism, especially if left without management, such as bony pains and muscular pains, increased risk of fractures, morphological abnormalities affecting bones and joints, and vascular and soft tissue calcification [19]. In a comparable study on dialysis patients, secondary hyperparathyroidism (PTH >300 pg/ml) was reported in 54% [20].

In the present study, the serum ferritin level was elevated. Similar results were reported in another study in which ferritin value was higher in patients with chronic pain due to arthropathy associated with dialysis [21].

Pain is a common complaint of patients on hemodialysis. However, little is known about its origin, frequency, and management. The reported frequency of pain varies widely in these patients with a mean pain prevalence of 47% and a range of 8%-82% [22]. Musculoskeletal pain was a main limiting factor for activities of daily living among the majority of patients on regular hemodialysis. It was referred to as the most disturbing pain [23].

Fibromyalgia syndrome was represented in more than half of the cases in this study (51.02%), which is much higher than what Couto et al. reported. FMS in their hemodialysis cohort had the same prevalence as in general population (3.9%). They, also, reported that FMS in their patients was associated with worse quality of life, depression and anxiety, and hence requires more attention by nephrologists [24]. FMS, in another study was significantly associated with a lower vitamin D level [25].

Arthralgia was present in 36.7% of the hemodialysis patients and arthritis in 10.2%. As a consequence of better survival of patients on long-term hemodialysis, the incidence of musculoskeletal complications such as arthritis, periarthritis and spondyloarthropathy is increasing [26]. The commonest complaint in dialysis patients was severe joint pain in the absence of radiological changes of arthritis in 41%, the shoulders usually being the most affected [4]. In another study, arthralgia was reported in 20% of patients on dialysis [27].

Flexor tenosynovitis was present in 28.6% and flexion deformities of the elbow in 16.3% and of the knees in 10.2%. Up to 80% of patients on dialysis had supraspinatus tendinitis [28]. Trigger finger, flexor tendon contracture, spontaneous tendon rupture and pathological fracture through amyloid bone cysts were reported in long-term regular haemodialysis for chronic renal failure [4].

Destructive spondylitis was present in 8.2% of the current patients on hemodialysis. Ultrasound examination in another study found at least one sign of enthesopathy in 50% of dialysis patients [29]. It is likely that more than third of the patients with chronic renal failure have achilles tendon abnormalities after a mean duration of hemodialysis of 6 years [30]. As previously mentioned, diagnosis of spondyloarthropathy in such patients is increasing as the survival on long-term dialysis improves [26]. Interestingly, in the study conducted by Hsu et al. none of their patients had spondyloarthritis, but they reported lumbar spondylosis in 0.7% of the cases [11].

End-stage renal disease is often associated with bone changes and soft-tissue calcifications [30]. Ectopic calcification was present in 24.5% of the patients in the current study. In another study, periarticular calcifications were reported in 5% of their patients [27]. In a case with CKD on hemodialysis, massive soft tissue calcifications were present with severe hyperparathyroidism secondary to end-stage renal disease [31] and in another long-term hemodialysis patient; massive ectopic, extraosseous painful calcifications occurred causing significant morbidity [32].

Recurrent cramps were present in 28.6% of the present patients and peripheral neuritis was found in 12.2%. Comparable results were

reported in the work of Chou et al. as muscle cramps were seen in 24% and symmetrical distal neuropathy in 18% [27].

Carpal tunnel syndrome was present in 14.3% of the current patients on regular hemodialysis. In another cohort, CTS had developed in 31% of patients, and was bilateral in half of them; at operation the presence of amyloid was confirmed [4]. Whereas, it has been reported to be only 6.3% and 9% in two other studies [27,28].

Amyloidosis was present in 8.2% of the hemodialysis cases. Dialysis-related amyloidosis is a clinical syndrome of pain, loss of function and other symptoms due to the deposition of amyloid consisting of β2-microglobulin in the musculoskeletal system. The condition is seen in patients who suffer from chronic kidney disease and are treated with hemodialysis for a long time [33]. Amyloid deposition occurs in multiple tissues with higher tendency towards bone and synovial membranes. Other tissues that can be affected with this serious complication include tendons and peripheral nerves [26]. As a result of this amyloid deposition, multiple musculoskeletal complications can develop such as carpal tunnel syndrome, arthralgias, bone cyst showing radiolucency at X-ray examination and destructive spondyloarthropathy [34]. Plain radiography demonstrates advanced dialysis-related amyloidosis findings such as bone erosions and cystic lesions, but it is not suitable for the demonstration of earlier changes [35].

Hepatitis C Virus (HCV) was positive in 16.3% of cases, rheumatoid factor present in 10.2% which were all females. In another study, a high prevalence of HCV infection (47.7%) was present in the hemodialysis patients. Incidence of HCV infection is increasing internationally, especially among patients maintained on hemodialysis. HCV is considered one of the major autoantibody stimulating viruses. Rheumatoid factor has been related to HCV but was gender independent [36].

Pain severity and symptom distress in dialysis patients are important, but underestimated and undertreated. They interfere with sleep quality and daily living. Routine assessment of pain burden, pain management and adequate analgesic use to treat specific dialysis-associated pain syndromes should be considered in guidelines [23].

Conclusion

Musculoskeletal complications are significant problems among hemodialysis patients and usually overlooked, especially in males. Increased awareness of the burden of these problems among health care providers helps to take them into consideration during management.

Conflicts of interest

None.

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