Exploring musculoskeletal disorders in end-stage kidney disease: A systematic review

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ABSTRACT

Introduction: This study focuses on the association between musculoskeletal disorders and chronic kidney disease (CKD), specifically end-stage kidney disease (ESKD). Its primary objective is to explore the spectrum of musculoskeletal disorders and to identify their prevalence rates and symptoms within diverse CKD subpopulations.

Materials and Methods: The screening process yielded 13 studies conducted in various countries and regions. These studies, employing designs such as cross-sectional, cohort, and clinical trials, focused on CKD patients across different stages, including early and late-stage CKD.

Results: The study revealed that musculoskeletal disorders are a considerable concern within the CKD population but are insufficiently explored among ESKD patients. Common musculoskeletal disorders identified include osteoarthritis, osteoporosis, fibromyalgia, carpopedal spasm, and chronic musculoskeletal pain syndrome. The prevalence of these disorders varied, with sub-group analysis revealing higher prevalence among hemodialysis patients compared to pre- and non-dialysis patients. While musculoskeletal pain remains consistent across CKD stages, potential confounding factors, such as palliative care settings and mobility issues warrant careful consideration.

Conclusion: The study underscores the importance of understanding and addressing musculoskeletal disorders in the CKD population, emphasizing the need for tailored interventions and future research endeavors.

KEYWORDS:
Musculoskeletal disorders, musculoskeletal pain, chronic kidney disease, end-stage kidney disease, hemodialysis patients

INTRODUCTION

Chronic kidney disease (CKD) is a leading cause of global mortality and has significantly contributed to the increasing burden of disability-adjusted life years (DALYs) over the past three decades. As of 2022, it is estimated that CKD affects more than 10% of the global population, impacting over 800 million individuals.[1-4] This condition is more prevalent among the elderly, women, ethnic minorities, and individuals with diabetes mellitus and hypertension. Globally, CKD poses a substantial burden, particularly in low- and middle-income countries (LMICs), where the age-standardized prevalence is 10.6% for men and 12.5% for women. Given the high prevalence of CKD and its associated adverse outcomes, there is an urgent need to enhance preventive measures and refine treatment strategies.[1-5]

Musculoskeletal disorders (MSD) are commonly associated with chronic kidney disease (CKD), including end-stage kidney disease (ESKD). MSD affects the bones, joints, muscles, and connective tissues, posing significant challenges due to altered bone metabolism, mineral imbalances, and other physiological changes linked to kidney dysfunction. Approximately 18 years ago, the Kidney Disease: Improving Global Outcomes (KDIGO) organization introduced a novel terminology to encompass this broad spectrum of clinical manifestations, termed Chronic Kidney Disease - Mineral and Bone Disorder (CKD-MBD). According to KDIGO 2017, CKD-MBD is characterized by: (i) abnormal metabolism of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D; (ii) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and (iii) soft-tissue calcifications, either vascular or extra-osseous. Patients with CKD-MBD frequently lack noticeable symptoms and typically present late. Many of these symptoms are non-specific, with the most frequent presentations including bone pain, arthralgia, proximal muscle weakness, tendinopathy, and spontaneous tendon rupture.[6]

Alterations in mineral metabolism and changes in bone structure are observable in all patients with CKD. In individuals undergoing dialysis, the entire musculoskeletal system—including bones, joints, muscles, tendons, and bursa—may be affected, with many patients showing signs of multiple types of musculoskeletal involvement.[7,8] The high burden of musculoskeletal diseases in this group can be attributed to several factors, including peripheral neuropathy, disrupted vitamin D metabolism,

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hyperparathyroidism, carnitine deficiency, aluminium toxicity, potassium imbalances (both hypo- and hyperkalaemia), acidosis, excessive iron accumulation, and severe hyperphosphatemia.[9]

Renal osteodystrophy, characterized by abnormal bone histology, is a key component of the bone abnormalities in CKD-MBD.[6] In CKD, abnormalities in bone remodelling, mineralization, and material properties develop, leading to significant decreases in structural strength, fractures, and deformities associated with long-term disease. Bone biopsy remains the gold standard for diagnosing and classifying renal osteodystrophy. Bone abnormalities in CKD can manifest as high turnover bone disease, adynamic bone disease, osteomalacia, and mixed uremic osteodystrophy.[6] These abnormalities result in increased bone fragility, leading to fractures. Therefore, understanding the prevalence and impact of musculoskeletal disorders in CKD patients is essential for providing comprehensive care and improving patient outcomes.

MATERIALS AND METHODS

Objectives

This study employs a systematic literature review to achieve two primary objectives (1) to explore the spectrum of disorders including osteoporosis, osteoarthritis, fibromyalgia, bone pain, and other relevant musculoskeletal conditions; and (2) to identify the range of prevalence rates of musculoskeletal disorders and main symptoms within various subpopulations of CKD patients. The secondary objective is to identify gaps and limitations in the current literature on musculoskeletal disorders in ESKD and to propose potential avenues for future research, including studies on novel therapeutic interventions, long-term outcomes of management strategies, and approaches tailored to specific patient subgroups.

Search strategy

A systematic literature search was conducted in the electronic databases PubMed, Embase, Scopus, and Cochrane Library. The search strategy utilised relevant keywords and Medical Subject Headings (MeSH) terms to comprehensively retrieve studies related to musculoskeletal disorders and ESKD.

Study selection criteria

The inclusion criteria encompassed studies that were published in peer-reviewed journals which involved adult individuals with CKD and/or musculoskeletal symptoms. Both observational studies (cross-sectional, cohort, case-control) and interventional studies (clinical trials, interventions) were considered. The exclusion criteria pertained to studies that were not published in English, those focusing exclusively on non-CKD populations, and studies with small sample sizes or incomplete data.

Data extraction, synthesis and analysis

The data extraction was conducted independently by three reviewers using a standardised form. The extraction fields included the study characteristics (author, year, country(ies), objective, design, sample size, patients' demographics), patients' CKD stage(s), musculoskeletal disorder types, prevalence rates, and the most common symptoms. A narrative synthesis approach was employed to summarise and integrate the findings across the selected studies.

Quality assessment

The quality of included studies was assessed using established tools such as the Newcastle-Ottawa Scale for Observational Studies and the Cochrane Collaboration Risk of Bias Tool for interventional studies. This assessment helped ensured the validity and reliability of the evidence synthesized. A critical appraisal was conducted for each study by two authors of this paper.

RESULTS

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the screening process is depicted in Figure 1.

Study characteristics

The 13 studies selected were conducted in Africa, Western Europe, East and West Asia. Four studies were undertaken in Egypt, and two in both France and Taiwan. Singular studies were conducted in Ethiopia, Spain, Denmark, and Iran. Furthermore, a comprehensive meta-analysis was included, encompassing data from 38 different countries. The predominant research method (11 out of 13 studies) was cross-sectional in nature. Additionally, there was one prospective cohort study and one meta-analysis, which incorporated data from 116 studies involving a total of 40,678 participants across 38 countries. The majority of the meta-analysis studies originated from the United States (18 studies) and the United Kingdom (12 studies). In the remaining 18 studies, the number of participants varied from 377 to 1169.[10] The participants were CKD patients over 18 years from both sexes (with a slight bias towards men) and mean ages ranging from 20[11] to 67.5.[12]

Patients' CKD stages

The 13 studies focused on different sub-populations with varying CKD stages. Seven studies focused on patients undergoing haemodialysis (different vintage),[12,13,14,15,7] including one study only with ESKD patients.[11] Two studies were done with pre-dialysis patients,[16,13] one study with patients with early and late-stage CKD not undergoing hemodialysis,20 and three studies with patients with different CKD stages undergoing dialysis or not.[17-19]

Musculoskeletal symptoms

The most common symptom recorded in the 13 studies was musculoskeletal pain which included arthralgia, myalgia, limb pain, and muscle weakness. The prevalence of arthralgia, which was the most common musculoskeletal manifestation, varied from 25.3%[12] to 83%[13], and it was reported across studies with patients with different CKD stages.

One study[13] with ESKD patients showed that the frequency of musculoskeletal symptoms increased with haemodialysis vintage, patients' age, and it was higher in men vs. women. Similarly, another study[12] showed, through logistic regression, that musculoskeletal symptoms were significantly associated

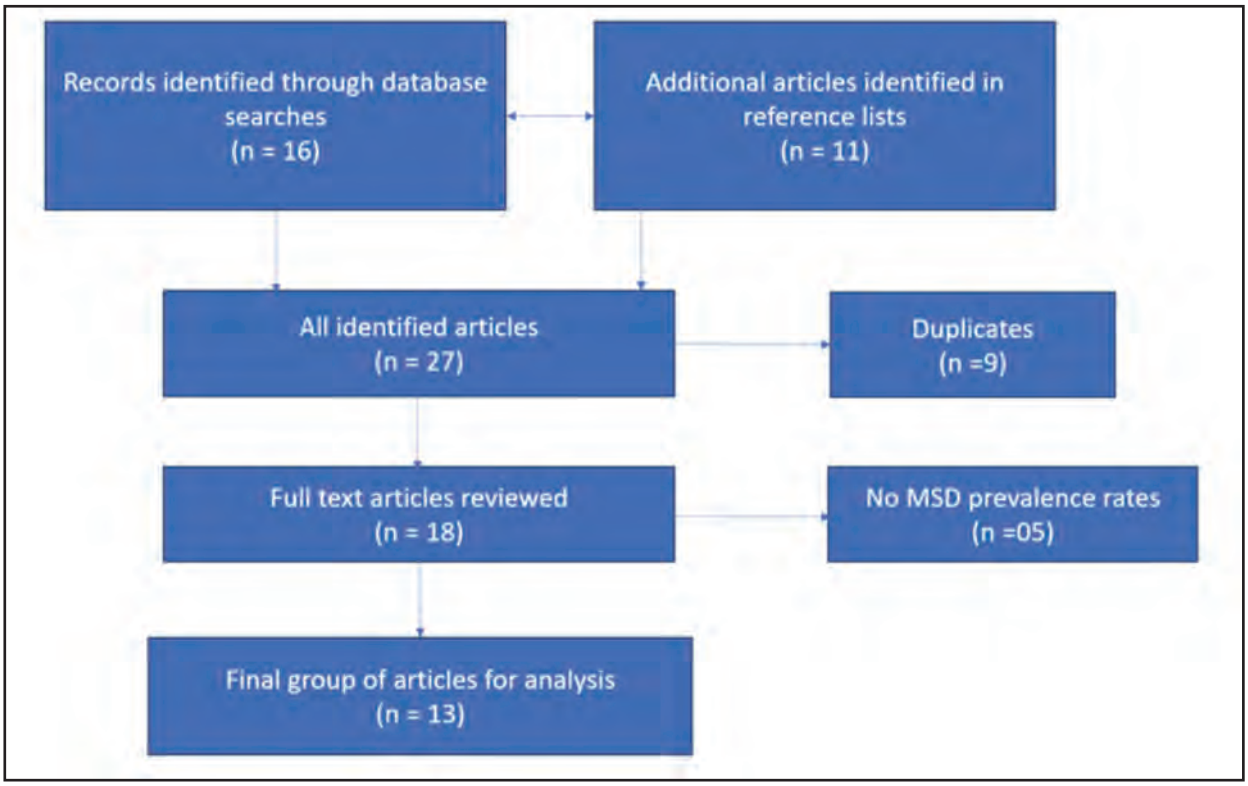

Fig. 1: PRISMA diagram of the screening process

with both dialysis vintage (odds ratio (OR) = 1.97; 95% CI 1.004–1.288, p = 0.044) and age (OR = 1.044, 95% CI 1.003–1.08, p = 0.035). The same study suggested that the threshold for the onset of musculoskeletal symptoms is around the seventh year of haemodialysis. Dialysis vintage was associated with the diagnosis of osteoarthritis, fractures, and chondrocalcinosis.

Several studies[16,20] have indicated that the prevalence of musculoskeletal pain remains consistent across all stages of CKD, suggesting no association between musculoskeletal pain and the risk of CKD progression. A potential confounding factor contributing to this outcome is the inclusion of CKD patients in stage 5 within palliative care settings, where chronic pain is actively managed.[19] Building upon this evidence, another study[10] contributed to further insight, demonstrating that chronic pain exhibits heightened severity in patients with advanced CKD.

Impaired mobility has also been correlated with musculoskeletal pain, as evidenced by a study conducted in Denmark[18] that compared CKD patients without mobility issues to the general population. Upon demographic matching, no difference in musculoskeletal pain was observed between CKD patients with mobility restrictions and the general population (61% and 63%, respectively; p=0.533).

Musculoskeletal disorders

The most common musculoskeletal disorders diagnosed clinically, as shown in the various studies were osteoarthritis (17.2%[13] and 53.9%[12]), osteoporosis (24.5%[11]), fibromyalgia (11%[19] and 51%[14]), carpopedal spasm (50.4%[7]), chronic musculoskeletal chronic pain syndrome (CMP) (38%)[11] and carpal tunnel syndrome (14.9%).[13] The most common radiologically diagnosed musculoskeletal disorders were secondary hyperparathyroidism (SHPT) diagnosed by X-ray[11] and Achilles Tendinopathy (67.9%), diagnosed by musculoskeletal ultrasonography (MSUS).[11]

Except for CMP, all musculoskeletal disorders were diagnosed among the haemodialysis population. One study[17] demonstrated, through logistic regression, that musculoskeletal disorders are most prevalent among women (AOR = 0.49; 95% CI 0.26, 0.94), with ages between 40-49 (adjusted odds ratio (AOR) = 3.34; 95% CI 1.07, 10.44) and CKD stages 3 (AOR = 0.24; 95% CI 0.06, 0.89) and stage 4 (AOR = 0.24; 95% CI 0.06, 0.89). Another study[11] similarly found that CMP was more prevalent in women compared to men (49 vs 28%, p<.001).

Prevalence rates

The prevalence of musculoskeletal disorders varied between 38%[11] and 90%[15]. This broad prevalence range can be attributed to differences in the definitions of musculoskeletal disorders, data collection methods, study designs, the scope of included musculoskeletal conditions, and the varying stages of CKD considered.

A sub-group analysis revealed that the highest prevalence of musculoskeletal disorders was found in studies with patients undergoing haemodialysis (60.4%[13] to 90.0%[15]) compared to pre-dialysis and CKD patients not undergoing dialysis (38.0%[9] to 64.0%[18]).

DISCUSSION

Musculoskeletal Symptoms

From the literature review, the most frequent musculoskeletal symptoms observed in various research studies were musculoskeletal pain, encompassing conditions like arthralgia (25.3%[12] to 83%[13]), myalgia, and limb discomfort reported across studies with patients with different CKD stages.

Chronic pain affects approximately 10–20% of the general adult population[21-24] with a notably higher prevalence among older women, with physical factors (such as obesity and other co-morbidities), emotional factors (like separation, divorce and widowhood), psychological factors (including anxiety and depression), and social factors (education, employment, and income) exerting significant influence.[23] Approximately 50–70% of these pain conditions are attributed to musculoskeletal origins, which would indicate that around 5–14% of the population experiences chronic musculoskeletal pain.[21-23]

Both patients undergoing dialysis[25-27] and those in the pre-dialysis stages of CKD[16,28,29] commonly experience musculoskeletal pain. Various factors can contribute to chronic musculoskeletal pain; potential culprits include gout, renal bone disease, and ischemic bone pain.[16,28] Research has demonstrated a significant connection between calcium × phosphate product levels and chronic musculoskeletal pain. Disruptions in calcium and phosphate balance, deficiency in vitamin D, and hyperparathyroidism have all been established as substantial underlying causes.[16,30]

Musculoskeletal Disorders

Osteoarthritis

The literature review showed that osteoarthritis was the most common musculoskeletal disorder among CKD patients. Within the CKD population, the prevalence of osteoarthritis surpassed that expected within the general population of similar age groups.[12,31] In these disorders, the knee joint was most frequently affected, followed by the ankle joint.[11,12,13,15,32]

Osteoporosis and fracture risk

Osteoporosis, characterized by a reduction in bone mineral density and deterioration of bone microarchitecture, is a significant concern in individuals with CKD. The literature review identified osteoporosis was diagnosed in one in four CKD patients.

The complex interplay of factors such as altered bone metabolism, hormonal imbalances, and mineral disturbances associated with kidney dysfunction contributes to the increased risk of osteoporosis in this population. Therefore, CKD patients are predisposed to fractures, adding a substantial burden to their overall health.

The risk of fractures in CKD is multifactorial, with factors such as mineral and bone disorders, impaired renal function, and comorbid conditions playing pivotal roles. Mineral imbalances, including disturbances in calcium and phosphorus metabolism, can compromise bone strength and integrity. SHPT, commonly observed in CKD, further exacerbates bone fragility. Additionally, the use of certain medications in the management of CKD, such as glucocorticoids, can contribute to bone loss and increase the susceptibility to fractures.[33-35] The consequences of fractures in CKD extend beyond the immediate physical impact, often leading to reduced mobility, impaired quality of life, and increased mortality risk.

Secondary Hyperparathyroidism

The most common radiologically diagnosed musculoskeletal disorders in the review was SHPT. The prevalence of SHPT in CKD is well-documented, with estimates ranging from 20% to 80%,[36] depending on the severity of the chronic kidney disease. SHPT emerges as a significant complication in the context of CKD, marked by high levels of blood parathyroid hormone (PTH). The development of SHPT in CKD is a result of abnormalities in various biochemical parameters, including elevated serum phosphorus and fibroblast growth factor 23 (FGF23), alongside reduced levels of serum calcium and vitamin D.[35]

SHPT emerges as the most prevalent diagnosis of musculoskeletal diagnosis detected radiologically.[11,16,33,34] Research indicates that anomalous radiographic indicators of SHPT escalate with the duration of dialysis. Common manifestations include sub-periosteal resorption of terminal phalanges, osteosclerosis (notably "rugger-jersey spine"), and the occurrence of brown tumors.[11,16,33,34]

Tendinopathies

Achilles Tendinopathy was also identified in the systematic review. Tendon tenderness and tendon ruptured have been reported in the literature among ESRD patients. The most common is Achilles tendon tenderness on palpations with prevalence varies between 11.9% to 44%.[37-38] Achilles tendinopathy was the most frequent condition detected MSUS followed by quadriceps and patellar tendinopathies.[11] The ultrasonographic abnormalities findings in Achilles tendinopathy include tendon thickness (>6mm), followed by reduction in echogenicity and the presence of calcified areas.[11,16] For quadriceps tendinopathy, the most prevalent abnormalities on MSUS were reduced echogenicity, followed by tendon thickness (>6 mm), and the presence of calcified areas.[11,37,39]

Renal Amyloidosis and Carpal Tunnel Syndrome

Dialysis-related amyloidosis (DRA) is a known dialysis complication with musculoskeletal involvement. In musculoskeletal DRA, there is a chronic accumulation of B2-microglobulin in the bone, muscle, periarticular cartilage, ligament and synovium. B2-microglobulin is a middle molecule of uremic toxins excreted in the urine. However, anuric patients on dialysis have a marked accumulation of these middle molecules due to poor removal during dialysis. The typical presentation is carpal tunnel syndrome (CTS), scapula-humeral peri-arthritis, tenosynovitis and bone cysts. Patients typically complain of numbness over the median nerve distribution and shoulder pain.[40] Jokar et al. reported a CTS prevalence of 24.3% in the haemodialysis population.[12]

Knowledge gaps and Limitations

In recent years, musculoskeletal disorders research in the context of CKD, including ESKD, has gained momentum, shedding light on the complex interplay between renal dysfunction and skeletal health. Despite the growing body of literature, notable gaps and limitations still exist, which warrant further investigation to comprehensively understand and effectively address the musculoskeletal challenges faced by individuals with ESKD.

A key area with a paucity of qualitative research is the realm of novel therapeutic interventions explicitly tailored for musculoskeletal disorders in ESKD. While there has been progress in elucidating the mechanisms underlying bone and muscle abnormalities in ESKD, innovative and targeted interventions to mitigate these issues remain limited. Another gap is the dearth of qualitative studies examining cutting-edge therapy interventions specifically designed for musculoskeletal issues in the ESKD population. This knowledge gap of efficient and focused interventions to address the complex musculoskeletal problems presented by ESKD patients remains because the majority of the published research concentrates on prevalence rates and related characteristics.

Additionally, the long-term outcomes of management strategies for musculoskeletal disorders in ESKD remain relatively under explored. Many existing studies tend to focus on short-term interventions and outcomes, leaving a gap in our understanding of the durability and sustainability of the implemented management approaches. Investigating the extended effects of interventions, and assessing their impact on long-term bone density, muscle function, and overall quality of life, could provide valuable insights into optimising treatment plans and refining therapeutic strategies for individuals living with ESKD-related musculoskeletal issues.

Furthermore, there is a knowledge gap about the implementation of management practices that are durable and sustainable because the majority of the research concentrates on short-term interventions and instant results.

Future Research Directions

An avenue with high potential for exploration is research tailored to specific patient subgroups within the ESKD population. The impact of musculoskeletal disorders can vary according to age, co-morbidities, and dialysis modality. Therefore, targeted investigations into how these factors interact with the musculoskeletal health of ESKD patients could unveil tailored intervention approaches. By accounting for these nuances, researchers can develop more precise and effective strategies to improve the quality of life for subgroups that might be disproportionately affected by musculoskeletal challenges.

Future research projects should give top priority to the creation and assessment of treatments that go beyond conventional management techniques. To address musculoskeletal problems in ESKD, novel treatments like pharmacological drugs, physical therapy, or regenerative strategies must be investigated in order to offer complete and customised solutions. Examining the effectiveness, safety, and patient compliance with these therapies may expand the range of treatments that are accessible and have a major influence on the quality of life for people with musculoskeletal issues associated with ESKD.

Moreover, future research endeavours ought to give precedence to longitudinal studies that monitor the prolonged impacts of therapies, evaluating their influence on the long-term quality of life, muscular function, and bone density of persons suffering from ESKD. This long-term methodology would offer significant insights into improving therapy approaches and treatment programmes for long-term gains in musculoskeletal health.

Lastly, studies that focus on particular patients' subgroups within the ESKD population are required. Musculoskeletal diseases can have different effects depending on age, gender, dialysis mode, and co-morbidities. Exact research on the interactions between these variables and musculoskeletal health in people with ESKD may provide specific management strategies. Researchers can create more targeted and effective interventions to enhance the quality of life for populations that may be disproportionately impacted by musculoskeletal issues by taking these subtleties into account. This method guarantees that interventions take into account the various demands of the ESKD population in addition to being effective.

CONCLUSION

Musculoskeletal disorders pose a substantial burden on CKD patients, exhibiting varied prevalence rates and associated symptoms across different stages of the condition. This systematic review aims to consolidate existing knowledge regarding musculoskeletal disorders in CKD patients, pinpoint gaps and limitations in current literature, and propose promising directions for future research. By addressing these gaps and exploring avenues such as innovative interventions, evaluating long-term outcomes, and adopting subgroup-specific approaches, the research community can enhance comprehension, management, and ultimately, the quality of life for individuals navigating the complex interplay of musculoskeletal health and CKD.

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