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REVIEW

Common musculoskeletal disorders in chronic liver disease patients

Rajat Ranjan, MD[1], Sanjiv Rampal, MBBS[2], Ashish Jaiman, MD[3], Mehmet Ali Tokgöz, MD[4], Jun Kit Koong, MD[5], Kamarajan Ramayah, MD[6], Ruveena Rajaram, MD[7]

[1]Integral Institute of Medical Sciences & Research, Integral University, Lucknow, Malaysia
[2]Department of Orthopaedics and Traumatology, Faculty of Medicine and Health Sciences, University Putra Malasia, Selangor, Malaysia
[3]Vardhman Mahavir Medical College & Safdarjung Hospital, Central Institute of Orthopaedics, New Delhi, India
[4]Ankara Keçiören Training and Research Hospital, Consultant Orthopaedic Surgeon, Ankara, Turkey
[5]Department of Surgery, Malaya University Medical Faculty, Kuala Lumpur, Malaysia
[6]Department of Surgery, University of Malaya Medical Centre, Kuala Lumpur, Malaysia
[7]Department of Medicine, University of Malaya Medical Centre, Kuala Lumpur, Malaysia

Chronic liver disease (CLD) is one of the most common ailments involving the hepatobiliary system. It is a common cause of mortality and morbidity worldwide. Liver cirrhosis is the end stage of CLDs characterized by scarring, architectural distortion, and progressive depletion of the liver's functional reserve.[1] Viral hepatitis and alcohol abuse are the most common causes of CLD with non-alcoholic steatohepatitis emerging as an important precipitating factor.[2]

Both CLD and cirrhosis are associated with numerous multi-system complications, including musculoskeletal diseases, hormonal, cardiac, and nervous system complications. Many factors

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Correspondence: Sanjiv Rampal, MBBS. Department of Orthopaedic, Faculty of Medicine and Health Sciences, University Putra Malaysia, 43400 Serdang, Selangor, Malaysia.

E-mail: rampalsurgery@gmail.com

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ABSTRACT

Chronic liver disease (CLD) is the commonest ailment affecting the hepatobiliary system. Six significant pathologies related to CLD include hepatic osteodystrophy (HO), increased infection susceptibility, sarcopenia, osteonecrosis of the femoral head (OFH), increased risk of periprosthetic complications and fracture. Hepatic osteodystrophy, which comprises osteopenia, osteoporosis, and osteomalacia, refers to alterations in bone mineral metabolism found in patients with CLD. The HO prevalence ranges from 13 to 95%. Low complement levels, poor opsonization capacity, portosystemic shunting, decreased albumin levels, and impaired reticuloendothelial system make the cirrhotic patients more susceptible to developing infectious diseases. Septic arthritis, osteomyelitis, prosthetic joint infection, and cellulitis were common types of CLD-associated infectious conditions. The incidence of septic arthritis is 1.5 to 2-fold higher in patients with cirrhosis. Sarcopenia, also known as muscle wasting, is one of the frequently overlooked manifestations of CLD. Sarcopenia has been shown to be independent predictor of longer mechanical ventilation, hospital stay, and 12-month mortality of post-transplantation. Alcohol and steroid abuse commonly associated with CLD are the two most important contributory factors for non-traumatic osteonecrosis. However, many studies have identified cirrhosis alone to be an independent cause of atraumatic osteonecrosis. The risk of developing OFH in cirrhosis patients increases by 2.4 folds and the need for total hip arthroplasty increases by 10 folds. Liver disease has been associated with worse outcomes and higher costs after arthroplasty. Cirrhosis is a risk factor for arthroplasty complications and is associated with a prolonged hospital stay, higher costs, readmission rates, and increased mortality after arthroplasty. Greater physician awareness of risk factors associated with musculoskeletal complications of CLD patients would yield earlier interventions, lower healthcare costs, and better overall clinical outcomes for this group of patients.

Keywords: Femur head necrosis, liver diseases, osteoporosis, sarcopenia.

predispose patients with CLD to musculoskeletal disorders. The intake of vitamins and minerals and the activation of vitamin D in the liver are impaired in CLD patients. Changes in endogenous steroid metabolism in the diseased liver and commonly used medications such as exogenous steroids, proton pump inhibitors, and diuretics eventually lead to bone loss in these patients. Current evidence has proven that cholestasis and non-regulated serum gamma-glutamyl transferase play also an important role in bone loss. As a result, all factors affecting the bone mineral metabolism are defined as hepatic osteodystrophy (HO). The prevalence of osteoporosis, which is a major global health problem, is reported as 10.3% among adults over the age of 50, besides prevalence rate rises to 21% in patients with chronic liver disease. Devastating fractures caused by low-energy trauma pose significant morbidity and mortality risks in HO patients.[3-5]

To the best of our knowledge, orthopedic manifestations of CLD have not been described under one heading in the literature. In this review, therefore, we comprehensively compiled all the orthopedic manifestations associated with CLD to increase the physician's general awareness and to avoid complications with early interventions. We identified six significant pathologies, including HO, increased infection susceptibility, sarcopenia, osteonecrosis of the femoral head (OFH), increased risk of periprosthetic complications, and fracture.

HEPATIC OSTEODYSTROPHY AND FRACTURE RISK

Hepatic osteodystrophy refers to the group of alterations in bone mineral metabolism found in patients with CLD. The umbrella of HO comprises osteopenia, osteoporosis, and osteomalacia.[3] The prevalence of HO ranges from as low as 13% to as high as 95%.[6,7] A higher prevalence is reported in the Indian population, i.e., from 68 to 95% versus 13 to 70% in Western countries.

Current studies have shown that almost 75% of patients with CLD have severe osteoporosis.[8,9] Hepatic osteodystrophy eventually results in the reduction of bone mineral density (BMD) and deterioration of the bone structure, for instance, trabecular architecture or bone geometry. These alterations in bone structure increase the risk of fragility fractures in patients with HO.[10,11] With alcoholism being an independent factor for the development of osteoporosis, overall, 35.9% of patients having alcoholic liver disease show altered bone metabolism and structure.[12,13]

In a study conducted by Choudhary et al.[14] with 115 cirrhosis patients with a mean age of 49 years on HO, which is one of the most common pathologies associated with CLD in the literature, only 4.5% of the patients had normal bone density and that osteoporosis (38.2%) or osteopenia (57.3%) was detected in all of the remaining patients. In the study conducted by Hajiabbasi et al.,[15] 97 patients with a mean age of 51 years were investigated, and vitamin D deficiency was found in 80.2% of the patients. Besides, 45.4% patients had osteopenia and 33% had osteoporosis. After adjusting for variables in a six-variable model, such as age, sex, body mass index (BMI), Child-Pugh score, current smoking status, estimated glomerular filtration rate (eGFR), and vitamin D level, lower vitamin D, higher Child-Pugh score, and lower eGFR values were reported to significantly increase the risk of abnormal dual-energy X-ray absorptiometry (DXA) results. Also, in a study conducted by Savic et al.[12] with 30 male patients, osteoporosis was detected in 20% of the patients and a statistically significant relationship between osteoporosis and disease severity and vitamin D status could not be determined.

Wang et al.,[16] in their study, demonstrated a significant association between non-alcoholic fatty liver disease and osteoporotic fracture risk in older Chinese men.[16] Tsai et al.[10] in their study of 4,000 patients with cirrhosis of mixed etiologies demonstrated an increased risk and cumulative increased incidence of fractures in such patients. Regardless of the etiology, the prevalence and severity of HO are positively correlated with the duration and severity of the liver disease. Several risk factors have been postulated for disease development including age, BMI, duration and severity of the underlying disease, overall low BMD with a history of fragility fractures, malnutrition, genetic predisposition, hormonal status, iron and copper accumulation, hyperbilirubinemia, alterations in vitamin status, and the effects of the used medications.[17] However, they neither give any information about the onset of HO nor about its severity. Early assessment of BMD by DXA, particularly of the lumbar spine and femoral neck, is essential to prevent fracture risk. Fracture risk can be minimized by correcting the reversible risk factors with early diagnosis of HO. Treatment and prevention strategies include lifestyle changes, dietary modifications, including stopping alcohol consumption, and medications (calcium/vitamin D/bisphosphonates).

Osteoporosis is usually asymptomatic. However, it increases the risk of bone fractures due to low-energy

traumas, particularly in the distal radius and proximal femur. Furthermore, in patients with alcoholic cirrhosis, the risk of fractures may be increased due to the direct effect of high levels of alcohol use or minimal hepatic encephalopathy. However, the absolute risk of hip fracture in individuals with cirrhosis is unknown due to the paucity of studies which measure the true incidence of fractures in CLD.[18]

INFECTIONS

Infections are commonly associated with CLD. Patients with CLD have impaired immunity and metabolic derangements. In patients with CLD, there is a breach in the intestinal portal barrier with bacterial overgrowth resulting in bacterial translocation. Also, low complement levels, poor opsonization capacity, portosystemic shunting, decreased albumin levels, and impaired reticuloendothelial system make the cirrhotic patients more susceptible to developing infectious diseases.[19] Septic arthritis, osteomyelitis, spondylodiscitis, prosthetic joint infection, cellulitis, and necrotizing fasciitis (NF) are the most common types of CLD-associated infectious conditions.[20,21]

Septic arthritis: The hip, knee, and shoulder are the most commonly affected joints in patients with CLD due to their abundant metaphyseal blood supply. The patient with septic arthritis presents with the usual symptoms of pain, swelling over the affected joint along with the limitation of range of motion and diagnostic management, also similar to non-CLD patients. Magnetic resonance imaging (MRI) plays an important part in the early detection of septic arthritis and guiding its subsequent treatment, thereby, preventing irreversible joint damage. Therefore, in patients with CLD and fever and limitation of joint movements, we should have a high suspicion of septic arthritis to diagnose and treat it promptly.[22]

In the study conducted by Hung et al.[23] 35,106 adult cirrhosis patients without a history of septic arthritis or prosthetic joints and 33,457 non-cirrhotic patients were followed for three years. The incidence of septic arthritis was approximately two-fold higher in patients with cirrhosis than patients without cirrhosis ($p=0.001$). Besides, it was found that the risk of developing septic arthritis increased by 1.5 times in patients with complicated cirrhosis, compared to other cirrhosis patients ($p=0.003$).

Spondylodiscitis/Osteomyelitis: In general, CLD patients have an increased incidence of bony infections, particularly of the spine, due to their lower immunity status.[24] Patients usually present with bony pain and swelling. In a study conducted by Kim et al.,[25] the increased rates of mortality in pyogenic vertebral osteomyelitis in cirrhotic patients were found, and liver function was a strong predictor of mortality in this group of patients. Diagnosis of spondylodiscitis is often delayed or missed due to the preexisting higher frequency of lower back pain in the general population. Therefore, hematological and radiological investigations should be ordered early to help in early diagnosis and to prevent complications. Diminished disc space is the first sign detected on X-ray. Loss of vertebral height and paravertebral abscesses are present in advanced disease. For spondylodiscitis, MRI is the investigation of choice with the decreased signal intensity from the disc and adjoining vertebral bodies on T1 weighted images and signal enhancement on T2 weighted images.[22]

Besides, tissue ischemia eventually leading to higher chances of peripheral gangrene and osteomyelitis can be observed in CLD patients as an adverse effect of advanced liver disease drugs, such as terlipressin.[26] The prevalence of skeletal tuberculosis is also higher in patients with cirrhosis. Therefore, there must be a high index of suspicion of extrapulmonary bony involvement in tubercular cirrhotic patients.[27]

Cellulitis: Cellulite, which is also common in the general population, occurs in approximately 12.5% of cirrhotic patients.[28] The risk of cellulite increases in patients with cirrhosis, and this risk further increases in complicated cases. Skin edema in the lower extremities is a common finding in patients with CLD, and chronic edema predisposes to infections.[29] In cirrhosis patients, skin erythematous disorders or other symptoms and/or signs of infection should be detected and treated early to prevent serious infectious diseases.[30] In the study by Lin et al.,[30] 39,966 patients with cirrhosis and 39,701 demographically-matched, randomly selected individuals were observed for three years, and cellulitis was statistically significantly higher in those with cirrhosis (6.7%) compared to the control group (4.0%) ($p<0.001$).

Necrotizing fasciitis: Necrotizing fasciitis is a rapidly progressive soft tissue infection that spreads along the fascial planes. It is most commonly a polymicrobial infection. Liver cirrhosis has been identified to be a common underlying disease for NF in many studies. In cirrhotic patients, NF is associated with a poor prognosis, despite advanced treatments currently. In a retrospective study of cirrhosis patients diagnosed with NF by Cheng et al.,[31] infection prognosis often

ended with death in patients with Grade C cirrhosis (p=0.028) and those with diabetes mellitus (p=0.043). In addition, Huang et al.[32] reported around nine-fold higher mortality rates of NF with cirrhosis compared to NF without cirrhosis.

SARCOPENIA

Sarcopenia, also known as muscle wasting, is one of the frequently overlooked manifestations of CLD. It is defined as a muscle mass two standard deviations below that of the mean muscle mass of healthy young adult reference groups.[22] It has a poor prognosis, as it is frequently associated with falls, fractures, and ineffective response to stresses including infections and surgeries. Sarcopenia is caused due to malnutrition frequently associated with CLD. Ineffective nutrient metabolization, inadequate oral intake due to early satiety associated with CLD, associated ascites and metabolic derangements are the key factors contributing to malnutrition.[33]

Sarcopenia has an impaired effort tolerance with a negative influence on the quality of life and survival; therefore, its early identification and appropriate management are crucial. Functional assessment of sarcopenia is performed by the handgrip strength and walking speed (WS). Currently, the European Working Group on Sarcopenia in Older People (EWGSOP) criteria and the Asian Working Group on Sarcopenia (AWGS) criteria define 0.8 m/s as the cut-off point for WS decline. In a study by Nishikawa et al.,[34] they categorized extracellular fluid excess based on the extracellular water-to-total body water ratio and found it to be closely linked to WS decline in CLD patients.[34]

Muscle mass has been objectively assessed by different techniques such as the bioimpedance analysis, DXA, computed tomography (CT), and MRI, out of which the L3 skeletal muscle index (L3SMI) expressed as cross-sectional muscle area height is found to be most useful. For calculating the L3SMI, a CT scan at the level of the third lumbar vertebra is analyzed with the help of commercially available software, which enables specific tissue demarcation using previously reported Hounsfield unit (HU) thresholds.[33]

In a study by Montano-Loza et al.[35] investigating the relationship between cirrhosis and sarcopenia on 120 patients with cirrhosis, L3SMI was measured, and sarcopenia was detected in 40% of the patients, and sarcopenia was reported to be a risk factor associated with mortality. Malnutrition and sarcopenia were shown to be independent predictors of longer mechanical ventilation, longer intensive care unit and hospital stay, increased incidence of infections, and 12-month mortality of post-transplantation in a study conducted by Kalafateli et al.[36] in 232 patients who underwent liver transplantation due to end-stage liver disease.

OF THE FEMORAL HEAD

Alcohol and steroid abuse commonly associated with CLD are the two main contributory factors for non-traumatic osteonecrosis. However, many studies have identified cirrhosis alone to be an independent cause of atraumatic osteonecrosis.[37-39] Various mechanisms have been postulated to demonstrate the association between cirrhosis and osteonecrosis, which include coagulopathy, endothelial dysfunction, and chronic inflammation.[38] Interleukin-33 and interleukin-6 (T-lymphocyte activators) have been linked to both cirrhosis and osteonecrosis along with the presence of hyperdynamic circulation in cirrhotic patients that facilitates diffusion of proinflammatory cytokines and endotoxins throughout the body.[40] The MRI is the investigation of choice, particularly in the early stages of OFH. Total hip replacement is the most routinely performed surgical procedure for OFH in cirrhotic patients. However, the absolute risks of surgery are markedly higher in these patients than in reference individuals.[41]

In the study conducted by Hung et al.,[38] which followed 40,769 cirrhotic patients and randomly selected 40,769 sex- and age-matched non-cirrhotic patients without baseline OFH for three years, OFH was detected in three of 1,000 cirrhotic patients and 1.1 of 1,000 patients in the control group (p<0.001, hazard ratio: 2.38). Besides, in a Danish Hip Arthroplasty Registry-based study which included 23,421 cirrhosis patients and 114,052 reference individuals, the risk of undergoing total hip replacement surgery due to OFH increased by 10-folds in cirrhotic patients.[41]

PERIPROSTHETIC COMPLICATIONS

Liver disease has been associated with worse outcomes and higher costs after arthroplasty. A number of studies have also identified cirrhosis as a risk factor for arthroplasty complications; cirrhosis is associated with a longer hospital stay, higher costs, readmission rates, and increased mortality after arthroplasty.[42] Increased rates of periprosthetic/peri-implant infections have been observed in patients with comorbidities such as cirrhosis.[43,44] The severity of liver damage is positively associated with higher rates of infections. In a study

performed by Jiang et al.,[45] as a nationwide status and investigating periprosthetic infections, the probability of periprosthetic infection in cirrhosis patients was 3.4-times increased ($p<0.001$) after total knee prosthesis, 5.4-times ($p<0.001$) after total hip prosthesis, and 5.8-times in prostheses performed after hip fracture ($p <0.001$). In the review by Onochie et al.,[46] 28,495 patients who underwent total hip arthroplasty were evaluated, and the infection rate was reported as 0.5% and the reoperation rate was 4% (46/1,083).

These patients usually present with pain and discharge around the operative site. Patients with cirrhosis have a longer length of hospital stay, increased costs, increased transfusion requirements, and higher rates of mortality, readmission, and reoperation. Also, higher rates of periprosthetic infections are reported in total knee arthroplasty compared to total hip arthroplasty. Among cirrhotic patients of total hip arthroplasty, higher rates of infection are reported for hip fractures (3.7%) than for non-hip fracture diagnosis (0.7%).[45-49]

In conclusion, the current review identifies multiple significant musculoskeletal complications related to CLD. The three most common complications associated with CLD are HO, infections (septic arthritis, spondylodiscitis, prosthetic joint infection), and sarcopenia. Greater physician awareness of risk factors associated with musculoskeletal complications of CLD patients would yield earlier interventions, lower cost of healthcare, and better overall clinical outcomes for this group of patients.

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