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MINIREVIEWS

Hepatocellular carcinoma and musculoskeletal system: A narrative literature review

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Abstract

Musculoskeletal alterations in hepatocellular carcinoma (HCC) are less common than liver-related complications. However, they can significantly impact the quality of life and overall prognosis of patients with HCC. The main obstacle in the clinical assessment of HCC-induced musculoskeletal alterations is related to effective and timely diagnosis because these complications are often asymptomatic and unapparent during routine clinical evaluations. This narrative literature review aimed to provide a comprehensive overview of the contemporary literature related to the changes in the musculoskeletal system in patients with HCC, focusing on its clinical implications and underlying etiopathogenetic mechanisms. Osteolytic bone metastases are the most common skeletal alterations associated with HCC, which could be associated with an increased risk of low-trauma bone fracture. Moreover, previous studies reported that osteopenia, sarcopenia, and myosteatosis are associated with poor clinical outcomes in patients with HCC. Even though low bone mineral density and sarcopenia are consistently reported as reliable predictors of pretransplantation and post-transplantation mortality in HCC patients, these complications are frequently overlooked in the clinical management of patients with HCC. Taken together, contemporary literature suggests that a multidisciplinary approach is essential for early recognition and clinical management of HCC-associated musculoskeletal alterations to improve patient prognosis. Further research into the mechanisms and treatment options for musculoskeletal complications is warranted to enhance our understanding and clinical management of this aspect of HCC.

Key Words: Hepatocellular carcinoma; Osteopenia; Osteoporosis; Sarcopenia; Bone metastases; Bone fragility

Core Tip: Musculoskeletal alterations have a powerful detrimental effect on the quality of life and prognosis of patients with hepatocellular carcinoma (HCC). The causes of HCC-induced musculoskeletal decline are complex and not yet fully understood. The biggest challenge in diagnosing HCC-related musculoskeletal changes is timely and effective diagnosis, as these alterations are often asymptomatic and may not be obvious during routine clinical evaluations. Therefore, a multidisciplinary approach to the clinical management of musculoskeletal alterations is essential in patients with HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, comprising 90% of patients with liver malignancy[1]. This type of malignancy typically develops due to end-stage chronic liver disease (around 80% of cases develop from cirrhosis)[2]. HCC rarely develops in the absence of liver cirrhosis or advanced liver fibrosis[3]. The highest incidence of HCC is found in Southeast Asia and North Africa where hepatitis B infection is endemic. In Western countries alcohol-associated and metabolic dysfunction-associated fatty liver disease and steatohepatitis are the predominant factors for HCC development[2,4-6].

Due to the aggressive nature of HCC, the prognosis of patients with HCC is poor (overall 5-year survival rate < 12%)[2], and HCC is the third leading cause of cancer-related deaths worldwide[1]. The estimated incidence of newly diagnosed patients with HCC is around 500000-1000000 per year, causing a global loss of 600000 lives each year[7]. Therefore, early identification of significant risk factors is essential to alter the disease course and improve patient survival and prognosis.

Screening programs for early detection of HCC improved survival in individuals with chronic liver disease who developed HCC[8]. Several prognostic systems have been developed over the years to identify the risk factors that could reveal poor prognosis in patients with HCC including[9]: The Barcelona Clinic Liver Cancer system[10]; the Cancer of the Liver Italian Program[11]; the Chinese University Prognostic Index score[12]; and the Child-Pugh score[10]. Still, all these scoring systems lack parameters considering the nutritional, functional, and performance status of patients with HCC[5]. Although long-term prognosis is dependent on the liver reserve and cancer staging[13], poor performance can significantly affect clinical outcomes in HCC patients. Therefore, the Eastern Cooperative Oncology Group scale was developed to provide an assessment of the performance and functional statuses in patients with HCC[14]. Recent advances in artificial intelligence-based risk calculations have enabled the integration of new risk factors that could significantly alter the clinical management of individuals with HCC[15].

The liver plays a central role in human metabolism, and patients with HCC are at a high risk of developing various complications. While the primary focus in the study of HCC traditionally revolves around liver-related complications (*e.g.*, hepatic encephalopathy, portal vein thrombosis, ascites, variceal bleeding, and obstructive jaundice), recent investigations have shed light on HCC-induced complications in other organs and systems, including the musculoskeletal system. HCC is almost three times more likely to appear in males than in females, with an incidence of 5.5/100000 in males and 2.0/100000 in females[2]. Thus, it is reasonable to predict that sex-specific distribution of musculoskeletal alterations (which are more common in postmenopausal females) could be shifted toward males with HCC.

In addition, it is known that the age distribution of patients with HCC is related to dominant viral hepatitis in the underlying population and the age at which it was acquired. However, it is important to note that HCC reaches its highest prevalence among individuals older than 65 years[2,7,16]. Considering that older age is a major risk factor for developing major musculoskeletal alterations (osteopenia, sarcopenia, and/or osteosarcopenia) and based on the global rise of an aging population[17-19], musculoskeletal complications are steadily becoming a major health concern in individuals with HCC.

Recognizing the importance of musculoskeletal health within the global health agenda, the Global Alliance for Musculoskeletal Health recently made substantial attempts to create a global roadmap for improving musculoskeletal health[20]. The first step on this journey is understanding the complexity of determinants that can affect musculoskeletal health and evaluating the particular health-burden contribution of each of these determinants in individuals who are healthy, aging, or with chronic diseases (Figure 1). Given that musculoskeletal complications are preventable, it is essential to fully understand the interconnections between HCC and musculoskeletal health, which can be beneficial for developing more effective and cost-efficient management strategies and increasing the quality of life for individuals with HCC (Figure 1).

This article aimed to provide a comprehensive narrative overview of the contemporary literature related to the changes in the musculoskeletal system in patients with HCC by focusing on its clinical implications and underlying etiopathogenetic mechanisms. Also, this review aimed to identify potential gaps in the current literature and suggest directions for future studies in HCC-associated musculoskeletal alterations.

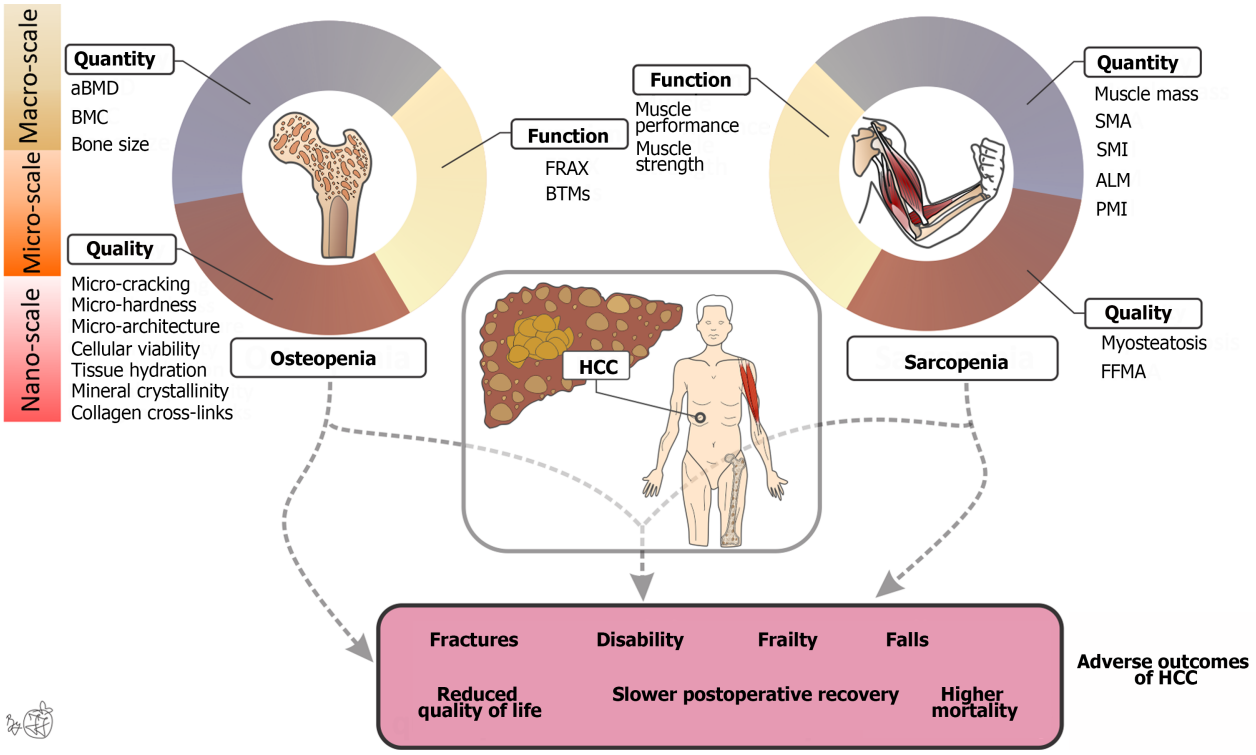

Figure 1 Role of musculoskeletal alterations in clinical management of patients with hepatocellular carcinoma. Various factors contribute to musculoskeletal decline in patients with hepatocellular carcinoma. A multiscale and multidisciplinary approach should be used to assess musculoskeletal health. aBMD: Areal bone mineral density; BMC: Bone mineral content; HCC: Hepatocellular carcinoma; FRAX: Fracture risk assessment tool; BTMs: Bone turnover markers; ALM: Appendicular lean mass; FFMA: Fat-free muscle area; PMI: Psoas muscle index; SMA: Skeletal muscle area; SMI: Skeletal muscle index.

LITERATURE SEARCH STRATEGY

An electronic search was performed using the PubMed/Medline, Embase, Cochrane, Web of Science, and CINAHL databases on November 25, 2023. To identify published articles on skeletal alterations in patients with HCC, we used the following search terms: "carcinoma, hepatocellular" OR "cancer, hepatocellular" AND "osteopenia" OR "osteoporosis" OR "bone mineral density" OR "bone metastases" OR "bone fracture". To identify published articles on muscular alterations in patients with HCC, we used the following search terms: "carcinoma, hepatocellular" OR "cancer, hepatocellular" AND "sarcopenia" OR "myosteatosis". Both authors independently reviewed the search results they obtained. Preclinical (basic science) and clinical studies written in English were included in this review. In cases of discrepancies, the dilemma was resolved through discussion, and both authors agreed with the final pool of studies included in the review.

SKELETAL-RELATED EVENTS IN PATIENTS WITH HCC

Bone metastases[21-24], pathological bone fractures[24,25], reduced bone mineral density (BMD)[26,27], hypercalcemia [28], and spinal cord compression[29] are among the most clinically relevant HCC-associated skeletal-related events.

The risk of bone metastasis in patients with HCC is not as prominent as in other common malignancies, such as gastric cancer, lung cancer, or breast cancer. There is a varying incidence of bone metastasis in patients with HCC of 3%-20%[30-32]. Substantial technological progress has been made in diagnosing and treating patients with HCC, which improved the overall survival rate, and bone metastases have become more commonly observed in recent years. Bone metastasis is reported in up to 38.5% of HCC patients at the initial diagnosis, while 11.7% of patients with HCC develop bone metastasis after surgical resection of the primary malignancy[4,33,34]. Moreover, the cumulative incidence of bone metastasis 1 year after diagnosis of extrahepatic disease in patients with HCC is 6.4%[35]. Bone metastasis in patients with HCC is most commonly diagnosed in the axial skeleton [vertebral column (up to 40%), pelvic bone, and ribs][31,34,36]. HCC-associated bone metastases are predominantly osteolytic (flake-like or erosion-like decline in bone density), but it could also be presented as osteoblastic metastasis and formation of expansive soft tissue mass[37,38].

Due to the aggressive disease course, studies investigating bone fractures in patients with HCC are very rare. Some data suggest that up to 13.2% of patients with HCC sustain bone fracture[25], but future well-designed large-scale prospective epidemiological studies are needed to analyze the fracture risk in patients with HCC. In cases when fracture risk analysis is not available, clinical surrogate markers of increased bone fragility are used to indirectly assess bone fracture risk. Reduced BMD (obtained by dual-energy X-ray absorptiometry) is widely accepted as a suitable surrogate marker in the clinical assessment of fracture risk[39,40]. According to recommendations by the World Health Organiz-

ation, individuals with a T score in the range between -1 to -2.5 are defined as those with osteopenia, while individuals with a T score lower than -2.5 are diagnosed with osteoporosis[41].

Although osteopenia and osteoporosis are commonly investigated in patients with various forms of chronic liver diseases[42], a recent shift has been directed at investigating HCC-associated BMD alterations (independent of bone metastasis)[26,27,43,44]. Sharma *et al*[43] demonstrated that vertebral BMD reduction, high tumor burden, and older age are important determinants of post-transplantation mortality in individuals with HCC. Miyachi *et al*[26] reported that preoperative low vertebral BMD was an independent risk factor for long-term outcomes after hepatectomy in male patients with HCC but not in female patients with HCC. Arguably, this sex specificity could be explained by the postmenopausal hormonal status of female subjects included in the study[26]. Most recently, Meister *et al*[44] and Müller *et al*[27] demonstrated that low BMD was associated with inferior survival in elderly patients with HCC undergoing partial hepatectomy or transarterial chemoembolization. These studies coherently implied that the integration of vertebral BMD measurement in a novel clinical algorithm could improve survival prediction and clinical management of patients with HCC and that using rehabilitation programs and specific antiresorptive therapy may further improve treatment outcomes among these individuals[26,27,43,44].

The current understanding of skeletal alterations in patients with HCC is limited by the small sample sizes in available retrospective studies as well as a modest number of these studies. Additionally, previous studies were conducted using vertebral BMD derived from multidetector computed tomography scans and not dual-energy X-ray absorptiometry, which is considered the "gold standard" in the clinical assessment of fracture risk. In addition, widely accepted up-to-date clinical methods used to assess skeletal status have certain limitations. For example, BMD is used as a two-dimensional surrogate marker of bone fragility even though it does not account for other intrinsic bone characteristics (bone quality; Figure 1). Moreover, BMD is in the physiological range in the majority of individuals with bone fractures, and anti-osteoporotic therapy has been reported to reduce fracture risk without affecting BMD[42]. Another important factor is the non-uniformity of the human skeleton, indicating that assessment of bone alterations in patients with HCC should be site specific.

Therefore, future studies should focus on resolving these limitations and on utilizing a hierarchical approach in analyzing the contribution of each bone fragility determinant in patients with HCC (Figure 1). The long-term benefit of multiscale and advanced assessment of bone fragility determinants could be creating a new patient-specific diagnostic algorithm that would provide a more accurate clinical assessment of the skeletal status in patients with HCC.

MUSCULAR ALTERATIONS IN PATIENTS WITH HCC

Recently, numerous research teams have begun studying age-related muscular alterations, which play a significant role in the deteriorating health and well-being of elderly individuals[45-47]. Muscular alterations are considered a natural course of aging[45-47], but these alterations could be exacerbated in various chronic comorbidities and malignancies. Among the most frequent muscular abnormalities that are prevalent in multiple tumors, including HCC, are sarcopenia[48-50] and myosteatosis[51,52]. Sarcopenia is a condition characterized by a loss of skeletal muscle mass and deterioration in muscle strength and function, while myosteatosis is characterized by intermuscular and intramuscular accumulation of adipose tissue[52].

A recent systematic review and meta-analysis revealed that the incidence rate of sarcopenia among patients with HCC was 42%[49]. However, there was substantial heterogeneity among the included studies (95% confidence interval: 0.36-0.48)[49]. The data suggested that 30%-40% of patients with HCC that developed from liver cirrhosis showed accelerated progression of sarcopenia at the time of diagnosis[51,53]. Also, the sex-specificity of HCC-associated sarcopenia was revealed in which the prevalence of sarcopenia was higher in studies that included predominantly male patients compared to studies conducted with fewer males (45% *vs* 37%, respectively)[49]. Lastly, the incidence rate of HCC-associated sarcopenia was reported to be higher in patients younger than 60 years when compared to older individuals [49,54]. Thus, previous studies suggest that sarcopenia could be a reliable predictor of inferior outcomes and lower survival rates in patients with HCC[55-59], possibly due to an increased risk of postoperative complications and reduced tolerance to chemotherapy.

Myosteatosis has initially been neglected in previous studies, but research interest in myosteatosis is currently increasing[52,59-62]. Previous data suggested a highly variable prevalence of myosteatosis among individuals with HCC (15.2%-38.8%)[52,60-62]. Patients with HCC-associated myosteatosis had a higher overall mortality rate compared to individuals with HCC who did not have myosteatosis[60]. Moreover, the 5-year cancer-specific survival rate after hepatectomy was significantly worse in individuals with myosteatosis in comparison to patients with HCC who did not have myosteatosis[61]. These studies suggest that myosteatosis could be associated with a reduced post-treatment survival rate in patients with HCC[52,60-62].

The current understanding of muscular alterations in patients with HCC is affected by the limited sample size in the available retrospective studies. These studies reported high variability and heterogeneity in the risk of developing muscular alterations in patients with HCC, suggesting that cautious interpretation of the pooled data is necessary. These studies used different diagnostic criteria when defining sarcopenia and myosteatosis, which indicates that a uniform and standardized diagnostic approach should be applied in future studies. Further, multiple muscles or groups of muscles should be utilized to accurately assess sarcopenia and myosteatosis. Muscle function, rather than muscle mass, could be an additional and powerful predictor that must be investigated in patients with HCC (Figure 1). Therefore, future well-designed clinical studies should focus on resolving these limitations to confirm the benefits of applying early screening and prevention measures (nutritional support and physical exercise). Since individuals with reduced muscle mass and/or

impaired muscle function have a greater risk of bone loss (osteosarcopenia), balance impairments, and fractures[46,63], clinical tools designed to simultaneously improve skeletal and muscle health are warranted in individuals with HCC.

ETIOPATHOGENETIC MECHANISMS LEADING TO MUSCULOSKELETAL ALTERATIONS IN HCC PATIENTS

Etiopathogenetic mechanisms leading to musculoskeletal alterations in patients with HCC are complex and not fully understood. Musculoskeletal alterations in patients with HCC are believed to result from the complex interplay between nutritional deficiencies, physical inactivity, hepatic dysfunction, hormonal/cytokine disruptions, and immunological imbalance (Figure 2), which could result in a loss of bone and muscle mass, impaired bone and muscular quality, bone and muscle tissue disorganization, and impaired musculoskeletal function[46,47,64].

The systemic proinflammatory milieu associated with HCC triggers the release of numerous cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-α, cyclooxygenases, and prostaglandin E2[44,49,65]. Increased concentrations of cytokines play a pivotal role in HCC-induced cachexia, muscle wasting, and bone resorption, perpetuating the musculoskeletal alterations observed in these patients. It is unclear whether the systematic and local HCC-induced proinflammatory environment accelerates bone loss through stimulation of osteoclastogenesis and activation of the Wnt/β-catenin pathway[51,66]. Liver dysfunction disrupts standard metabolic mechanisms and hormonal regulation, causing a decline in the serum concentrations of insulin-like growth factor-1 and sex hormones (especially unbound testosterone), thereby displaying a negative effect on the musculoskeletal system[49].

It has been commonly believed that the interaction between the skeletal and muscular systems is primarily mechanical. However, recent studies have demonstrated that bone and muscle tissues have additional endocrine and paracrine functions enabling complex bidirectional bone-muscle crosstalk[46,47]. Local and systematic effects of bone-muscle crosstalk are the foundation for understanding osteosarcopenia in individuals with various chronic liver diseases[46,47,67,68], including HCC (Figure 2). Muscles release secretory factors known as myokines, that are implicated in positively or negatively affecting the bone independent of mechanical loading. Insulin-like growth factor-1, fibroblast-like growth factor 2, myostatin, irisin, brain-derived neurotrophic factor, osteoglycin, osteoactivin, IL-6, IL-7, and IL-15 are examples of bone-affecting myokines[46,51,69]. Myostatin, IL-6, and follistatin can facilitate the systemic hyperinflammatory state caused by HCC, especially in HCC that developed from advanced liver fibrosis and liver cirrhosis[51,70]. In addition, HCC can affect cellular processes, leading to cell autophagy, oxidative stress, and mitochondrial dysfunction, ultimately leading to musculoskeletal atrophy[49,71].

Currently, there are only a few known bone-derived factors that influence skeletal muscles. Osteokines secreted by osteoblast or osteoclasts and vascular endothelial growth factor derived by bone marrow mesenchymal cells are two examples. Further research into this field is needed[46]. Vascular endothelial growth factor is a crucial angiogenesis-driving factor in the primary HCC lesion as well as in osteolytic bone metastasis[4,24,34]. It has an activating effect on bone resorption through the OPG-RANKL pathway[44,72,73].

Some studies that suggest that the immunological nature of musculoskeletal alterations in HCC are based on poorly understood interactions between the skeletal, muscular, and immune systems and the HCC lesion[44,74]. It is hypothesized that certain anti-resorptive drugs may display significant anti-tumor effects *via* various immunological pathways [44]. It should be noted that changes in cellular metabolism and mitochondrial dysfunction are possible links in cancer-induced cachexia and musculoskeletal alterations[75,76]. These data indicate possible therapeutic value of various factors contributing to cellular oxidative metabolism in patients with HCC-associated musculoskeletal alterations, warranting further research[76,77].

Since understanding multifactorial etiopathogenetic mechanisms responsible for HCC-associated musculoskeletal alterations is still limited, future research should focus on resolving this complex interconnection. These new insights may lead to the development of new cutting-edge therapeutic modalities specifically designed to alleviate the musculoskeletal burden in patients with HCC.

CONCLUSION

Musculoskeletal alterations in HCC, though less common than liver-related complications, can significantly impact the quality of life of patients with HCC. Frequent musculoskeletal alterations associated with HCC are bone metastases, osteosarcopenia, and myosteatosis. However, these complications are frequently overlooked in the clinical management of patients with HCC. Due to the limited data regarding HCC-induced musculoskeletal alterations and its etiopathogenetic mechanisms, further multidisciplinary research on HCC-associated musculoskeletal alterations is needed to provide better clinical management and treatment options and to improve the quality of life in patients with HCC. Considering that individuals with lower bone mass are more likely to present with impaired muscle function and that individuals with impaired muscle function will develop skeletal impairment, clinical tools designed to simultaneously improve skeletal and muscle health are warranted in individuals with HCC.

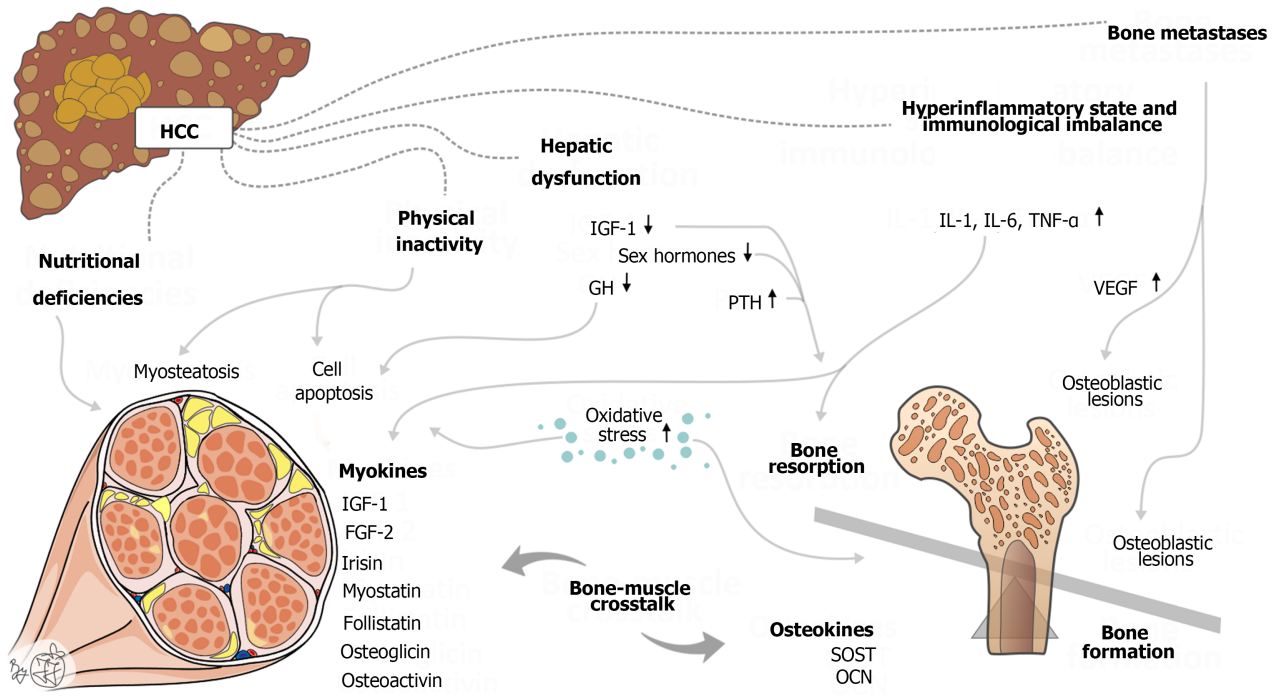

Figure 2 Schematic representation of possible etiopathogenetic mechanisms of musculoskeletal alterations in patients with hepatocellular carcinoma. The possible roles of multiple factors leading to musculoskeletal alterations in patients with hepatocellular carcinoma are shown. HCC: Hepatocellular carcinoma; IGF-1: Insulin-like growth factor 1; FGF-2: Fibroblast-like growth factor 2; GH: Growth hormone; IL: Interleukin; PTH: Parathyroid hormone; OCN: Osteocalcin; SOST: Sclerostin; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.

FOOTNOTES

Author contributions: Jadzic J conceptualized the study, wrote the initial draft, and conducted the visualization; Jadzic J and Djonic D acquired the data; Djonic D reviewed and edited the manuscript; and all authors read and approved the final version of the manuscript.

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