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A Narrative Review Of Sarcopenia And Hepatocellular Carcinoma

Nada Hussin Hantool[1], faisal khalid alghamdi[2], Turki Hamood Alotaibi[3], Ayman Muneer Fataa Alharbi[4], Shujaa Safar Share Alotaibi[5], Nasser Khalid Nasser AlOtaibi[6], Ahmed Abdullah Alluqmani[7], Saud Homoud Aldagani[8], Sultan Lafi Qaed Alosaimi[9], Mohammed Saad Ateeq Alotaibi[10], Mazen Munir Matar[11], Fuad Atiah Banan Zalah[12]

Abstract

Hepatocellular carcinoma (HCC) is a prevalent and aggressive cancer often accompanied by sarcopenia, a condition of reduced muscle mass and function. This narrative review explores the complex relationship between sarcopenia and HCC, emphasizing its impact on prognosis and treatment outcomes. We discuss the mechanisms underlying sarcopenia in HCC, including inflammation, hormonal imbalances, and elevated ammonia levels. Established and emerging therapeutic targets are explored, with a focus on ghrelin mimetics, pro-inflammatory cytokine modulation, and growth differentiation factor-15 (GDF-15). The review highlights the negative influence of sarcopenia on HCC treatment effectiveness, including surgery, ablation, radiation, and targeted drugs. We conclude by summarizing promising therapeutic options for sarcopenia management in HCC patients, including testosterone replacement therapy, vitamin D supplementation, and exercise interventions.

Introduction

A global health concern, hepatocellular carcinoma (HCC) affected an estimated 905,700 individuals in 2020, with 830,200 succumbing to the disease, making it the third most common cause of cancer-related mortality worldwide. Chronic infections (hepatit[1]is B and C viruses), toxins (alcohol), and nonalcoholic fatty liver disease are established risk factors for HCC. Notably, most HCC diagnoses occur in individuals with pre-existing cirrhosis, often a consequence of these very risk factors. This association between NAFLD, cirrhosis, and HCC extends further, with a higher prevalence of sarcopenia, a condition of reduced muscle mass and physical function, observed in these patient populations (1).

[1]Pharmacy Technician, Primary Health Care Center Aljadi, Saudi Arabia.
[2]pharmacist Technician, Aljumom Health Sector Ministry Of Health, Makkah, Saudi Arabia
[3]Pharmacy Technician, Compliance Assist Administration , Compliance Third West Office , Al Duwadimi , Saudi Arabia
[4]Pharmacy Technician, Starh PHC, Saudi Arabia.
[5]technician Pharmacy,Hejrrat Al-Mashaan Healthcare Center- Taif, Saudi Arabia.
[6]technician Pharmacy,Irada And Mental Health Complex In Jeddah - Irada Services, Saudi Arabia.
[7]technician Pharmacy,Raibgh Health Center, Saudi Arabia.
[8]Pharmacy Technician, Medical Supplies And Warehouses, Saudi Arabia.
[9]Technician Pharmacy,Al Bajadia General Hospital, Saudi Arabia.
[10]Technician Pharmacy, Dawadmi General Hospital, Saudi Arabia.
[11]Technician-Pharmacy,MOH MAKKAH, Saudi Arabia.
[12]pharmacy Technician,Medical Supply, Saudi Arabia.

The high prevalence of sarcopenia in HCC and chronic liver disease (CLD) warrants a comprehensive review of the existing literature (2). Early identification and targeted interventions for sarcopenia hold promise for improving patient outcomes (3). This includes potentially mitigating symptom burden, enhancing quality of life (QoL), and increasing tolerance to anti-neoplastic therapies in HCC patients (4).

HCC and sarcopenia share a common link: a chronic pro-inflammatory state that fuels disease progression. This inflammatory response, often observed in solid tumors, is thought to induce a combination of anorexia, fatigue, and muscle wasting. Meta-analyses confirm the high prevalence of sarcopenia in HCC, with a pooled estimate of 41.7% across 57 studies (5). However, prevalence can vary depending on assessment methods, geographic location, and disease stage. Notably, for solid tumors in general, the prevalence is higher in the palliative setting (49.2%) compared to curative (39.6%), while HCC shows a narrower difference (38.2% vs 35.4%) (6). This narrative review aims to equip clinicians with the latest information for improved identification, assessment, and management of patients with co-existing HCC and sarcopenia.

A review of literature

Definition and Diagnoses

Cancer patients frequently experience muscle wasting, a hallmark of co-existing conditions like sarcopenia, cachexia, and frailty, especially in older adults (7). Furthermore, the detrimental effects of excess fat alongside muscle loss (sarcopenic obesity) and intramuscular fat infiltration (myosteatosis) necessitate careful evaluation in these patients.

Sarcopenia, diagnosed clinically, is characterized by loss of muscle mass and function. Dual-energy X-ray absorptiometry (DXA) or computed tomography (CT) scans are used for measurement, with cut-offs adjusted for factors like race and sex. While typically associated with aging (primary sarcopenia), it can also be a secondary consequence of diseases like cancer.

The European Working Group on Sarcopenia in Older People 2 (EWGSOP2) refined the 2018 consensus definition, emphasizing low muscle strength as the cornerstone of sarcopenia (8). Low muscle mass and quality support the diagnosis, while poor physical performance signifies severe cases. The updated F-A-C-S clinical algorithm streamlines assessment, and EWGSOP2 provides clinically relevant cut-offs for these variables, including physical performance. Furthermore, the validated SARC-F questionnaire, a 5-item self-assessment tool focusing on strength, mobility, and falls, is recommended for initial screening (9). In a study of oncology patients, one-third screened positive for sarcopenia using the SARC-F, and these individuals experienced higher functional impairment, poorer quality of life, and increased mortality (10).

Building on the SARC-F screen, clinicians can further assess muscle strength using hand grip strength (HGS) measured by dynamometer or the chair stand test (time to rise from a seated position five times without using arms). HGS is convenient and correlates well with overall muscle function (11). The FNIH Biomarkers Consortium established cut-off points for weakness (<26 kg grip strength for men and <16 kg for women), which align with those proposed by EWGSOP2 (12). The combined importance of HGS and muscle mass is highlighted in a study of liver cancer resections. Patients with both low HGS and reduced muscle mass had significantly longer hospital stays ($P<0.001$) and more frequent readmissions ($P=0.02$) compared to other groups (13). These findings underscore the value of comprehensive sarcopenia assessment.

While various techniques assess muscle quantity, each has limitations and advantages. DXA and CT scans are most common, with cut-offs adjusted for sex and race. Magnetic resonance imaging can also accurately assess sarcopenia in CLD, with abbreviated protocols reducing scan time and contrast use (14). DXA offers rapid appendicular muscle mass measurement with low radiation exposure. In DXA studies, sarcopenia is defined as an appendicular skeletal muscle mass index (muscle mass divided by height squared) two standard deviations below values from healthy young adults. Cut-offs for appendicular lean mass by DXA adjusted for body mass index (BMI) are similar for FNIH and EWGSOP2 (<0.789 for men, <0.512 for women) (11, 14). CT scans offer a convenient opportunity to assess body composition during routine diagnostic or restaging procedures. Regional fat and lean tissue analysis at the 3rd lumbar vertebra strongly predicts whole-body composition (15). Notably, while most studies focus on this level, a preliminary report suggests CT measurements of the psoas muscle at a different level may be prognostic for survival in HCC patients (15).

While DXA, CT, and MRI provide the gold standard for muscle mass assessment, bioelectrical impedance analysis (BIA) offers a less accurate but radiation-free and cost-effective alternative. A systematic review of 24 BIA studies (n=3,607 patients) showed promise. In five studies, BIA performed comparably to other sarcopenia screening methods, while 14 studies linked BIA-identified sarcopenia with poorer patient outcomes (16). Additionally, BIA-derived phase angle measurements have been shown to predict hospitalization, falls, and mortality in cirrhotic outpatients (17). These findings suggest BIA may be a valuable tool for sarcopenia evaluation, particularly in resource-limited settings.

Ultrasound emerges as a promising, non-invasive tool for sarcopenia assessment in liver disease according to a recent review (18). This analysis of 10 studies primarily focused on large leg and arm muscles, with half including HCC patients. The majority demonstrated a link between US-derived muscle measurements and clinical outcomes. One HCC study even showed a significant correlation between skeletal muscle index (SMI) and lower limb subcutaneous fat using US (19). However, the lack of a universally accepted reference standard limits clear comparisons across these studies.

Following muscle mass assessment, physical performance tests gauge sarcopenia severity. A recent meta-analysis revealed a 2-9% prevalence of severe sarcopenia depending on region and classification (20). Common tests include gait speed, the Short Physical Performance Battery (SPPB), and the Timed-Up-and-Go (TUG) test. Hand grip strength and SPPB are prevalent in both geriatrics and oncology research, with the SPPB demonstrating significant correlation with survival, particularly in older adults (21). For example, a low SPPB score (<10) predicts poorer outcomes in leukemia, lung cancer, and liver cirrhosis (21). Standardizing sarcopenia diagnosis and adhering to published guidelines are crucial for reducing research heterogeneity (20).

Factors that lead to sarcopenia

Sarcopenia arises from a lifetime of accumulating muscle dysfunction. Beyond aging, "secondary sarcopenia" affects many older adults with comorbidities or lifestyle factors that deplete muscle mass. Examples include malignancies, chronic inflammation, organ dysfunction, malnutrition, and inactivity (bed rest). Disordered protein metabolism, characterized by decreased synthesis and increased degradation, underlies sarcopenia. While potential therapeutic targets exist within these mechanisms, they are interconnected. For instance, inflammation can contribute to both hormone resistance and autonomic dysfunction. CLD often co-occurs with or precedes HCC and shares similar pathways leading to sarcopenia. The relationship, however, is complex. Notably, sarcopenia is independently associated with

non-alcoholic steatohepatitis and advanced fibrosis, even without obesity, inflammation, or insulin resistance (22). Uncertainties remain regarding whether sarcopenia precedes NAFLD progression or arises as a complication due to worsening liver disease. Emerging evidence suggests a shared pathophysiological pathway along the muscle-liver-adipose axis for NAFLD and sarcopenia, potentially indicating a bidirectional relationship where NAFLD contributes to sarcopenia development (23).

Muscle Loss and Liver Disease

Muscle loss triggers a vicious cycle. It reduces insulin sensitivity, liver glycogen storage, and protein synthesis, while promoting fat breakdown. Fatty liver accumulation (steatosis) is fueled by chronic inflammation from fat tissue. Reduced muscle mass and its signaling molecules further worsen liver fat accumulation. Importantly, ectopic fat in the liver and muscle (myosteatosis) seems to be more directly linked to liver damage than muscle mass itself.

Mechanisms of Sarcopenia

Several mechanisms contribute to sarcopenia in this context, including:

- Inflammation
- Hormonal imbalances
- Elevated blood ammonia levels
- Disrupted nervous system function

Hyperammonemia, a potential culprit, disrupts muscle function, increases muscle breakdown, and contributes to cognitive decline. Aging itself weakens muscles and reduces muscle-building hormones (1).

Therapeutic Targets

Ghrelin, a gut hormone stimulating appetite, shows promise. Studies suggest it improves liver function in animal models. Anamorelin, a drug mimicking ghrelin's effects, is being explored to combat muscle loss (24).

Pro-inflammatory cytokines are additional targets. These signaling molecules promote muscle breakdown. Other potential markers for diagnosing and monitoring sarcopenia severity are being investigated (1).

Growth differentiation factor-15 (GDF-15) is another area of interest. Linked to muscle loss and potentially a biomarker for fatty liver disease, it's being studied as both a marker and therapeutic target in clinical trials (1).

Beta-blockers and alterations in the gut microbiome are emerging areas of research for treating sarcopenia (1).

Anti-Cancer Treatments

Anti-cancer drugs like tyrosine kinase inhibitors used for HCC can worsen muscle loss. Studies suggest poorer outcomes in patients with sarcopenia receiving this treatment (1).

Prognosis of Sarcopenia in HCC

Sarcopenia offers independent prognostic value in HCC. Cirrhosis and HCC patients with sarcopenia experience worse clinical outcomes. Interestingly, sarcopenia in cirrhotic patients may even predict the development of HCC itself. A study found male cirrhotics with sarcopenia had a significantly increased risk of future HCC development (25).

Sarcopenia significantly worsens outcomes in cirrhotic patients. A meta-analysis linked it to higher mortality risk (26). Complications like hepatic encephalopathy and sepsis are also more frequent with sarcopenia. Following liver transplantation, sarcopenia is associated with poorer outcomes, including longer hospital stays, ventilation dependence, and increased mortality (27). Radiologically measured muscle mass at the third lumbar vertebra, when combined with the MELD score, improves prognostic evaluation in HCC patients awaiting transplant (28). Moreover, the presence of both sarcopenia and obesity (visceral fat measured by CT scan) significantly increases post-transplant mortality in acutely ill cirrhotic patients, even after accounting for other factors (29). These findings highlight sarcopenia as a crucial factor for risk stratification in cirrhotic patients. Sarcopenia significantly hinders HCC treatment effectiveness. A large meta-analysis revealed its presence in over 40% of HCC patients (3). Across various therapies like surgery, ablation, radiation, and targeted drugs, sarcopenia correlated with poorer outcomes, including lower survival rates, higher recurrence rates, and increased treatment side effects (3). Notably, the negative impact of sarcopenia is amplified in patients with cirrhosis, suggesting a synergistic effect (3). Supporting these findings, a multi-center surgical study showed that patients with sarcopenia were less likely to achieve "Textbook Outcomes" (no complications, readmission, extended stays) after HCC resection (30). These positive short-term outcomes, in turn, predicted better long-term survival and recurrence-free survival (30). Similarly, a study combining muscle mass and strength assessments found that patients with both low measures had significantly higher complication rates and healthcare costs after surgery (31).

Therapy

While no single medication is currently approved for sarcopenia, promising therapeutic options are emerging from clinical trials. Anamorelin, a drug approved in Japan for cancer cachexia that increases lean body mass and appetite, holds the most promise for wider application due to its oral administration (32). However, caution is warranted regarding its specific benefit for sarcopenia, as a large clinical trial showed improved lean body mass but not handgrip strength (32). A recent review explored various pharmacological interventions for sarcopenia, including testosterone, growth hormones, and myostatin inhibitors. While some drugs increased muscle mass, they often lacked improvements in physical function, a crucial outcome (33). Other promising agents in pre-clinical development include metformin, exerkines (signaling molecules promoting exercise benefits), and senolytics (drugs targeting senescent cells). Currently available options with established safety profiles include testosterone and vitamin D.

While no definitive solution exists, several promising therapies are emerging for sarcopenia in HCC patients. Testosterone replacement therapy shows promise, with studies demonstrating improved muscle mass, bone mass, and hemoglobin in men with cirrhosis and advanced solid tumors (34, 35). However, specific evaluation in HCC patients is lacking. Vitamin D supplementation is another reasonable recommendation due to its low risk profile and association with sarcopenia, particularly in patients with CLD and vitamin D deficiency (36, 37). However, clinical trial results regarding vitamin D's isolated benefit are inconsistent, as it's often combined with other interventions like exercise (38). Meta-analyses suggest combining vitamin D with exercise and protein supplementation may enhance muscle mass

and physical function (39, 40). Additionally, the form of vitamin D supplementation may influence outcomes, with calcifediol potentially impacting muscle strength (41). Further research is needed to determine optimal treatment strategies for sarcopenia in this patient population.

Conclusion

Sarcopenia is a prevalent and concerning complication in HCC patients, significantly impacting prognosis and treatment outcomes. Early identification and intervention for sarcopenia hold promise for improving patient outcomes in HCC. Future research efforts should focus on optimizing treatment strategies to address muscle loss and improve the overall well-being of HCC patients.

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