# Sarcopenia and Osteosarcopenia in CLD

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The liver plays a pivotal role in nutrient/energy metabolism and storage, anabolic hormone regulation, ammonia detoxification, and cytokine production. Impaired liver function can cause malnutrition, hyperammonemia, and chronic inflammation, leading to an imbalance between muscle protein synthesis and proteolysis. Patients with chronic liver disease (CLD) have a high prevalence of sarcopenia, characterized by progressive loss of muscle mass and function, affecting health-related quality of life and prognosis. Recent reports have revealed that osteosarcopenia, defined as the concomitant occurrence of sarcopenia and osteoporosis, is also highly prevalent in patients with CLD. Since the differentiation and growth of muscles and bones are closely interrelated through mechanical and biochemical communication, sarcopenia and osteoporosis often progress concurrently and affect each other. Osteosarcopenia further exacerbates unfavorable health outcomes, such as vertebral fracture and frailty. Therefore, a comprehensive assessment of sarcopenia, osteoporosis, and osteosarcopenia, and an understanding of the pathogenic mechanisms involving the liver, bones, and muscles, are important for prevention and treatment.

Keywords: chronic liver disease ; sarcopenia ; osteoporosis ; osteosarcopenia

## 1. Introduction

Sarcopenia is a syndrome characterized by decreased muscle mass and function (strength and/or physical performance) [1][2][3][4][5]. In 1989, Rosenberg proposed the concept of sarcopenia as the age-related loss of muscle mass [6]. Later research emphasized that loss of muscle function is important for diagnosing sarcopenia, which can occur regardless of age [1][2][3][4][5]. The European Working Group on Sarcopenia in Older People (EWGSOP) has classified sarcopenia into primary (when no other cause exists other than aging) and secondary (when the condition is caused by underlying diseases such as chronic liver disease (CLD)) [1]. The liver is a multifunctional organ involved in glucose and energy metabolism, hormonal regulation, cytokine production, and ammonia detoxification. Impairment of liver function can cause malnutrition, hyperammonemia, chronic inflammation, and imbalance of muscle protein synthesis and proteolysis, leading to sarcopenia [5][7]. Thus, sarcopenia is highly prevalent in patients with CLD, especially those with liver cirrhosis (LC) (30–70%) [8]. Notably, sarcopenia negatively affects health-related quality of life and prognosis, and increases the risk of complications, such as infection [9][10].

Several studies revealed a close relationship between sarcopenia and osteoporosis in community-dwelling older adults. This finding has fueled the concept of osteosarcopenia, defined as the concomitant occurrence of sarcopenia and osteoporosis [11][12][13][14]. These two musculoskeletal disorders affect each other and share a common genetic, mechanical, and biochemical pathophysiology [15][16][17][18]. Osteosarcopenia has been associated with more negative health outcomes than either sarcopenia or osteoporosis alone, increasing the risk of falls, fractures, and mortality [19]. Therefore, it has been described as a “hazardous duet” [19]. Our recent studies revealed that osteosarcopenia frequently develops and is associated with fractures, low physical performance, and frailty in patients with CLD [20][21][22]. Although sarcopenia and osteosarcopenia are a global health concern, appropriate assessment and early diagnosis of these musculoskeletal disorders in patients with CLD remain inadequate in real-world clinical settings. Furthermore, treatment strategies for osteosarcopenia in CLD have yet to be established, limiting our understanding of the pathogenic mechanisms involving the liver, bones, and muscles in patients with CLD.

## 2. Osteosarcopenia in Chronic Liver Disease

### 2.1. Prevalence and Clinical Significance of Osteosarcopenia in Patients with Chronic Liver Disease

In 2009, Binkley and Buehring advocated the concept of sarco-osteoporosis, which was then defined as the concomitant occurrence of sarcopenia and osteoporosis and has now evolved into the term “osteosarcopenia” [14]. Patients with osteosarcopenia have an increased risk of falls and fractures, resulting in a poor quality of life and increased mortality [23][24]. The prevalence of osteosarcopenia in community-dwelling older adults is 8.4 %, 12.7%, and 19.2 % in Japan, China,

and Korea, respectively [11][12][13]. In a Korean study of patients aged ≥60 years with hip fractures, the prevalence of osteosarcopenia was 28.7%, and the 1-year mortality of osteosarcopenia (15.1%) was higher than that of the normal (7.8%), osteoporosis-alone (5.1%), and sarcopenia-alone (10.3%) groups [25]. Furthermore, patients with osteosarcopenia had higher scores for disability, frailty, and depression than those without it [13]. A recent pooled analysis of the aging general population demonstrated that osteosarcopenia increases the risk of fractures [odds ratio (OR), 2.46], falls (OR, 1.62), and mortality (OR, 1.66) [26].

As shown in **Table 1**, several studies have investigated the prevalence and clinical significance of osteosarcopenia in patients with CLD [20][21][22][27][28]. In one study of 142 patients with LC, the proportion of patients in the normal, sarcopenia-alone, osteoporosis-alone, and osteosarcopenia groups was 53.5%, 12.0%, 12.7%, and 21.8%, respectively [20]. In the osteosarcopenia group, the values of the skeletal muscle mass index (SMI) and handgrip strength were the lowest, whereas the prevalence of vertebral fractures was the highest (61.3%) among all four groups [20]. In another study of 117 patients with primary biliary cholangitis (PBC), the prevalence of osteosarcopenia was 15.4% [21]. Patients with osteosarcopenia had a higher prevalence of vertebral fractures than those without osteoporosis and sarcopenia (55.6% vs. 6.7%) [21]. In the other study of 291 patients with CLD, 49 (16.8%) and 81 (27.8%) had osteosarcopenia and frailty, respectively [22]. Frailty and vertebral fractures more frequently occurred in patients with osteosarcopenia than in those without (79.6% vs. 17.4% and 59.2% vs. 20.2%, respectively) [22]. Patients with osteosarcopenia also showed a greater impairment of physical performance and balance than those without osteosarcopenia, resulting in an increased risk of falls and fractures [29]. Furthermore, vertebral and hip fractures can cause impaired physical function and immobility, thereby leading to sarcopenia [30][31]. These findings suggest that osteosarcopenia and fractures are closely interrelated and exacerbate the negative health outcomes of each other.

**Table 1.** Representative previous studies on osteosarcopenia in patients with chronic liver disease.

| Authors (Year, Country) [Reference] | Patients Characteristics | Prevalence of Osteosarcopenia | Diagnostic Method for Osteosarcopenia (Criteria for Sarcopenia) | Main Findings |
|---|---|---|---|---|
| Hayashi et al. (2018, Japan) [27] | 112 patients with CLD (LC, 36.0%) | 7.1% | DEXA and BIA (JSH) | Sarcopenia and LC were significantly associated with the BMD. Sarcopenia (OR, 6.16) and LC (OR, 15.8) were independent risk factors for osteoporosis. |
| Bering et al. (2018, Brazil) [28] | 104 patients with CHC | — | DEXA (EWGSOP) | Low BMD, low muscle strength, pre-sarcopenia, and sarcopenia were noticed in 34.6%, 27.9%, 14.4%, and 8.7% of subjects, respectively. Appendicular skeletal muscle mass was an independent predictor of BMD. Sarcopenia was independently related to bone mineral content. |
| Saeki et al. (2020, Japan) [21] | 117 patients with PBC (LC, 9.4%) | 15.4% | DEXA and BIA (JSH) | The SMI and handgrip strength were significantly correlated with the BMD. Patients with osteosarcopenia had a higher prevalence of vertebral fracture (55.6%) than those without both sarcopenia and osteoporosis (6.7%). |
| Saeki et al. (2020, Japan) [22] | 291 patients with CLD (LC, 51.9%) | LC 20.5% Non-LC 12.9% | DEXA and BIA (JSH) | Frailty was an independent risk factor associated with osteosarcopenia (OR, 9.837), and vice versa (OR, 10.069). The prevalence of frailty and vertebral fracture was significantly higher in patients with osteosarcopenia than in those without osteosarcopenia (79.6% vs. 17.4% and 59.2% vs. 20.2%, respectively). |

*Abbreviations: BIA, bioelectrical impedance analysis; BMD, bone mineral density; CHC, chronic hepatitis C; CLD, chronic liver disease; DEXA, dual-energy X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; JSH, Japan Society of Hepatology; LC, liver cirrhosis; OR, odds ratio; PBC, primary biliary cholangitis; SMI, skeletal muscle mass index.*

### 2.2. Pathogenic Mechanisms of Osteosarcopenia: Relationship between Muscle and Bone

Given that muscles and bones are closely related during their development and growth, it is conceivable that sarcopenia, osteoporosis, and osteosarcopenia often progress in conjunction with each other [15][16][17][18]. Therefore, an understanding of the relationship between muscles and bones along with the underlying pathogenesis of osteosarcopenia

is essential from a therapeutic point of view. Although the pathogenesis of osteosarcopenia in CLD is not fully elucidated, we addressed the possible mechanisms herein.

#### 2.2.1. Mechanical Factors

Increasing the mechanical load on the skeletal muscles leads to protein synthesis and muscle hypertrophy, while the opposite causes muscle atrophy [32]. The maintenance of bone mass and strength depends on the contribution of the following skeletal muscle-derived mechanical forces: (1) the tensile forces generated by contracting muscles at their insertion site; (2) the compressive forces between bones generated by muscles contracting through joints; and (3) the bending forces that long bones receive when the muscles generate the force to lift the object held distally [32]. The expression level of IGF-1, which has a positive effect on muscles and bones, is increased by exercise-induced mechanical loading [17]. Accordingly, reduced physical activity cannot maintain skeletal muscle and bone mass, resulting in the development and progression of sarcopenia and osteoporosis.

#### 2.2.2. Genetic Factors

During embryogenesis, muscles and bones originate from a common mesenchymal precursor, and their development is controlled by common genes and growth factors [33]. Therefore, genetic factors may influence both sarcopenia and osteoporosis. A genome-wide association study (GWAS) of Han Chinese and US Caucasians revealed that three single nucleotide polymorphisms in or near the glycine-N-acyltransferase (*GLYAT*) gene, which is essential for the regulation of glucose and energy metabolism, were associated with bone size and muscle mass [34]. A subsequent GWAS in the US identified *METTL21C* as a pleiotropic gene for bones and muscles [35]. *METTL21C* is highly expressed in muscles and plays an important role in myoblastic differentiation, calcium homeostasis, and survival of osteocytes against apoptosis through the modulation of NF-κB signaling [17][35]. In addition, myocyte enhancer factor 2C (*MEF-2C*) and α-actinin 3 (*ACTN3*) are candidate genes with a pleotropic effect on bones and muscles [36]. MEF-2C is a transcriptional regulatory protein involved in skeletal muscle development, sarcomeric gene expression, and fiber-type control; loss of MEF-2C results in disorganized myofibers [37]. MEF-2C also regulates bone homeostasis by modulating osteoclastic bone resorption, and deletion of *MEF-2C* results in increased bone mass [38]. *ACTN3* is highly expressed in fast glycolytic muscle fibers and contributes to the differentiation of muscle fibers toward the fast-twitch type [39]. Additionally, *ACTN3* is expressed in osteoblasts, and the deletion of *ACTN3* reduces bone mass [40].

#### 2.2.3. Chronic Inflammation

The production of reactive oxygen species (ROS) and proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, is increased in chronic disease conditions, including CLD [41][42]. Chronic inflammation inhibits protein synthesis and osteoblast differentiation and promotes protein breakdown and osteoclastic bone resorption, which lead to skeletal muscle and bone mass loss [5][17]. Advanced glycation end products (AGEs), which are induced by non-enzymatic glycation, oxidation, and chronic inflammation, suppress the expression of myogenic genes and impair the osteoblasts' function, thereby affecting the quality of bone produced [17][43]. Pentosidine is one of the major AGEs and its well-characterized cross-link has been studied in bone tissues. The levels of pentosidine increases with age, and high levels of pentosidine are a risk factor for fractures in older adults. Serum pentosidine levels were reported to be negatively correlated with skeletal muscle mass in postmenopausal women with diabetes [44]. Notably, plasma pentosidine levels were increased in patients with a decreased liver functional reserve as well as in those with prevalent fractures [45]. Similar to other pathological conditions, CLD (especially LC) also facilitates a reduction in both skeletal muscle mass and bone mass and quality.

#### 2.2.4. Myokines

Skeletal muscle cells secrete various endocrine molecules, such as IGF-1, myostatin, irisin, beta-aminoisobutyric acid (BAIBA), fibroblast growth factor 2 (FGF2), IL-6, IL-7, IL-15, and osteoglycin, which influence bone metabolism [15][16][17][18]. IGF-1 is synthesized primarily in the liver and is also produced by muscles and bones [17]. As described above, IGF-1 regulates skeletal muscle protein synthesis via the PI3K/AKT/mTOR pathway. Moreover, IGF-1 stimulates osteoblast proliferation and contributes to the maintenance of bone mass and strength [46][47]. When CLD progresses to the advanced stages, serum IGF-1 levels decrease, leading to a loss of skeletal muscle and bone mass [48][47]. As described above, myostatin acts as a negative regulator of muscle cell proliferation and protein synthesis and is inhibited by IGF-1 and testosterone. Serum myostatin levels have not only been revealed to be higher in patients with decompensated LC than in those with compensated LC and healthy controls, but have also been associated with muscle mass loss and worse survival [49][50]. Notably, myostatin also negatively regulates bone formation and metabolism by promoting osteoclast differentiation [51]. Inhibition of the myostatin pathway results in an increase in not only muscle mass but also bone mass [52]. Irisin, a hormone-like myokine produced by skeletal muscles in response to physical exercise, is released

into the circulation by cleavage of the fibronectin type Ⅲ domain-containing protein 5 (FNDC5) and plays a crucial role in the regulation of bone metabolism [53][54]. Administration of recombinant irisin increases cortical bone mass and strength and promotes pro-osteoblastic genes and osteoblastic bone formation, and it also reduces the effect of osteoblast inhibitors [55]. Intriguingly, irisin is highly expressed in hepatocytes, Kupffer cells, and sinusoidal endothelial cells in the human liver [56]. This suggests that CLD may decrease irisin levels that may subsequently affect bone mass and strength. Among patients with LC, it was revealed that not only were the serum irisin levels lower in sarcopenic patients than in non-sarcopenic patients, but also associated with sarcopenia [54]. FNDC5 deficiency impairs autophagy and fatty acid oxidation and enhances lipogenesis in the liver via the AMPK/mTOR pathway [57]. BAIBA, a small molecule secreted by skeletal muscles during exercise, protects osteocytes against ROS-induced apoptosis and prevents bone loss [58].

#### 2.2.5. Osteokines

As bones secrete various substances that affect other organs, they may also be considered as endocrine organs. Bones secrete various osteokines such as osteocalcin, sclerostin, Wnt, TGF-β, fibroblast growth factor 23 (FGF23), and prostaglandin E2 (PGE2), which affect the metabolism of not only bones but also muscles [15][16][17][18]. Osteocalcin is a noncollagenous protein secreted from osteoblasts [59]. Osteocalcin-deficient ($Ocn^{-/-}$) mice showed reduced muscle mass, and treatment with exogenous osteocalcin increased muscle mass in older mice, whereas deletion of osteocalcin resulted in increased bone mass [60][61]. In contrast, another study using newly generated $Ocn^{-/-}$ mice demonstrated that osteocalcin was not involved in the regulation of bone quantity and muscle mass [62]. Therefore, the impact of osteocalcin on muscles and bones remains controversial. The Wnt/β-catenin signaling pathway promotes osteoblast differentiation and osteogenesis and is involved in prenatal myogenesis and skeletal muscle regeneration/fibrosis [63][64]. Sclerostin, a protein encoded by the Sost gene and produced by mature osteocytes, acts as a negative regulator of the Wnt/β-catenin pathway, and therefore inhibits bone formation [65]. In patients with PBC, sclerostin was found to be expressed in the bile duct epithelium and was associated with the severity of cholangitis. In addition, the serum sclerostin levels in patients with PBC were higher than those in controls, suggesting its potential involvement in impaired bone formation [66]. A Korean study of healthy non-diabetic subjects showed that serum sclerostin levels were negatively correlated with skeletal muscle mass [67]. However, sclerostin-deficient mice showed greater trabecular bone volume and lower muscle mass than did wild-type mice [68]. Therefore, further studies are needed to clarify the role of sclerostin in the muscle–bone relationship. TGF-β, which is produced by osteoblasts and involved in the regulation of bone remodeling and homeostasis [69], induces muscle fiber atrophy by upregulating the E3 ubiquitin ligase atrogin-1 in mice [70]. In a mouse model of osteolytic bone metastases, bone-derived TGF-β contributed to muscle weakness by decreasing $Ca^{2+}$-induced muscle force production [71].

#### 2.2.6. Vitamin D

The liver plays a crucial role in vitamin D metabolism. When the liver's function is impaired, bone and muscle homeostases are dysregulated through vitamin D metabolism [72][73]. Vitamin D is not only involved in the intestinal absorption of calcium and phosphate and maintenance of appropriate circulating concentrations of these minerals, but also contributes to normal bone mineralization [72][73]. Vitamin D deficiency causes secondary hyperparathyroidism, leading to an increased bone turnover and consequent bone loss. An in vitro study of $C_2C_{12}$ skeletal muscle cells reported that vitamin D promoted the differentiation of myogenic cells by increasing the expression and nuclear translocation of the vitamin D receptor (VDR) and modulating promyogenic and antimyogenic factors [74]. VDR knockout and vitamin D-deficient mice showed decreased muscle mass and strength, dysregulation of myogenic regulatory factors, and increased myostatin and MuRF1 [75]. Reportedly, the rate of patients with CLD who frequently exhibited vitamin D deficiency (≤20 ng/mL) ranged from 47% to 87% [76]. In one study of patients with CLD, serum vitamin D levels were positively correlated with skeletal muscle mass and handgrip strength, and low vitamin D levels were associated with sarcopenia [77]. Our study revealed that low vitamin D levels, especially severe vitamin D deficiency (≤10.5 ng/mL), were closely related to sarcopenia and frailty in patients with CLD [76]. These findings suggest that maintaining sufficient levels of vitamin D is important for preventing loss of skeletal muscle and bone mass.

## References


1. Cruz-Jentoft, A.J.; Baeyens, J.P.; Bauer, J.M.; Boirie, Y.; Cederholm, T.; Landi, F.; Martin, F.C.; Michel, J.P.; Rolland, Y.; Schneider, S.M.; et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010, 39, 412–423.
2. Cruz-Jentoft, A.J.; Bahat, G.; Bauer, J.; Boirie, Y.; Bruyère, O.; Cederholm, T.; Cooper, C.; Landi, F.; Rolland, Y.; Sayer, A.A.; et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing 2019, 48, 16–31.

3. Chen, L.K.; Liu, L.K.; Woo, J.; Assantachai, P.; Auyeung, T.W.; Bahyah, K.S.; Chou, M.Y.; Chen, L.Y.; Hsu, P.S.; Krairit, O.; et al. Sarcopenia in Asia: Consensus report of the Asian Working Group for Sarcopenia. J. Am. Med. Dir. Assoc. 2014, 15, 95–101.
4. Chen, L.K.; Woo, J.; Assantachai, P.; Auyeung, T.W.; Chou, M.Y.; Iijima, K.; Jang, H.C.; Kang, L.; Kim, M.; Kim, S.; et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. J. Am. Med. Dir. Assoc. 2020, 21, 300–307.
5. Nishikawa, H.; Shiraki, M.; Hiramatsu, A.; Moriya, K.; Hino, K.; Nishiguchi, S. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): Recommendation from the working group for creation of sarcopenia assessment criteria. Hepatol. Res. 2016, 46, 951–963.
6. Rosenberg, I.H. Summary comments: Epidemiological and methodological problems in determining nutritional status of older persons. Am. J. Clin. Nutr. 1989, 50, 1231–1233.
7. Kim, Y. Emerging Treatment Options for Sarcopenia in Chronic Liver Disease. Life 2021, 11, 250.
8. Dasarathy, S.; Merli, M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J. Hepatol. 2016, 65, 1232–1244.
9. Kim, G.; Kang, S.H.; Kim, M.Y.; Baik, S.K. Prognostic value of sarcopenia in patients with liver cirrhosis: A systematic review and meta-analysis. PLoS ONE 2017, 12, e0186990.
10. Hanai, T.; Shiraki, M.; Nishimura, K.; Ohnishi, S.; Imai, K.; Suetsugu, A.; Takai, K.; Shimizu, M.; Moriwaki, H. Sarcopenia impairs prognosis of patients with liver cirrhosis. Nutrition 2015, 31, 193–199.
11. Kobayashi, K.; Imagama, S.; Ando, K.; Machino, M.; Ota, K.; Tanaka, S.; Morozumi, M.; Kanbara, S.; Ito, S.; Ishiguro, N.; et al. Epidemiology and effect on physical function of osteosarcopenia in community-dwelling elderly people in Japan. Mod. Rheumatol. 2020, 30, 592–597.
12. Wang, Y.J.; Wang, Y.; Zhan, J.K.; Tang, Z.Y.; He, J.Y.; Tan, P.; Deng, H.Q.; Huang, W.; Liu, Y.S. Sarco-Osteoporosis: Prevalence and Association with Frailty in Chinese Community-Dwelling Older Adults. Int. J. Endocrinol. 2015, 2015, 482940.
13. Park, K.S.; Lee, G.Y.; Seo, Y.M.; Seo, S.H.; Yoo, J.I. Disability, Frailty and Depression in the community-dwelling older adults with Osteosarcopenia. BMC. Geriatr. 2021, 21, 69.
14. Binkley, N.; Buehring, B. Beyond FRAX: ItSrs time to consider “sarco-osteopenia”. J. Clin. Densitom. 2009, 12, 413–416.
15. Li, G.; Zhang, L.; Wang, D.; AlQudsy, L.; Jiang, J.X.; Xu, H.; Shang, P. Muscle-bone crosstalk and potential therapies for sarco-osteoporosis. J. Cell. Biochem. 2019, 120, 14262–14273.
16. Brotto, M.; Bonewald, L. Bone and muscle: Interactions beyond mechanical. Bone 2015, 80, 109–114.
17. Kawao, N.; Kaji, H. Interactions between muscle tissues and bone metabolism. J. Cell. Biochem. 2015, 116, 687–695.
18. Yang, Y.J.; Kim, D.J. An Overview of the Molecular Mechanisms Contributing to Musculoskeletal Disorders in Chronic Liver Disease: Osteoporosis, Sarcopenia, and Osteoporotic Sarcopenia. Int. J. Mol. Sci. 2021, 22, 2604.
19. Hirschfeld, H.P.; Kinsella, R.; Duque, G. Osteosarcopenia: Where bone, muscle, and fat collide. Osteoporos. Int. 2017, 28, 2781–2790.
20. Saeki, C.; Takano, K.; Oikawa, T.; Aoki, Y.; Kanai, T.; Takakura, K.; Nakano, M.; Torisu, Y.; Sasaki, N.; Abo, M.; et al. Comparative assessment of sarcopenia using the JSH, AWGS, and EWGSOP2 criteria and the relationship between sarcopenia, osteoporosis, and osteosarcopenia in patients with liver cirrhosis. BMC. Musculoskelet. Disord. 2019, 20, 615.
21. Saeki, C.; Oikawa, T.; Kanai, T.; Nakano, M.; Torisu, Y.; Sasaki, N.; Saruta, M.; Tsubota, A. Relationship between osteoporosis, sarcopenia, vertebral fracture, and osteosarcopenia in patients with primary biliary cholangitis. Eur. J. Gastroenterol. Hepatol. 2021, 33, 731–737.
22. Saeki, C.; Kanai, T.; Nakano, M.; Oikawa, T.; Torisu, Y.; Abo, M.; Saruta, M.; Tsubota, A. Relationship between Osteosarcopenia and Frailty in Patients with Chronic Liver Disease. J. Clin. Med. 2020, 9, 2381.
23. Kirk, B.; Zanker, J.; Duque, G. Osteosarcopenia: Epidemiology, diagnosis, and treatment-facts and numbers. J. Cachexia Sarcopenia Muscle 2020, 11, 609–618.
24. Salech, F.; Marquez, C.; Lera, L.; Angel, B.; Saguez, R.; Albala, C. Osteosarcopenia Predicts Falls, Fractures, and Mortality in Chilean Community-Dwelling Older Adults. J. Am. Med. Dir. Assoc. 2021, 22, 853–858.
25. Yoo, J.I.; Kim, H.; Ha, Y.C.; Kwon, H.B.; Koo, K.H. Osteosarcopenia in Patients with Hip Fracture Is Related with High Mortality. J. Korean. Med. Sci. 2018, 33, e27.

26. Teng, Z.; Zhu, Y.; Teng, Y.; Long, Q.; Hao, Q.; Yu, X.; Yang, L.; Lv, Y.; Liu, J.; Zeng, Y.; et al. The analysis of osteosarcopenia as a risk factor for fractures, mortality, and falls. Osteoporos. Int. 2021. online ahead of print.

27. Hayashi, M.; Abe, K.; Fujita, M.; Okai, K.; Takahashi, A.; Ohira, H. Association between sarcopenia and osteoporosis in chronic liver disease. Hepatol. Res. 2018, 48, 893–904.

28. Bering, T.; Diniz, K.G.D.; Coelho, M.P.P.; Vieira, D.A.; Soares, M.M.S.; Kakehasi, A.M.; Correia, M.I.T.D.; Teixeira, R.; Queiroz, D.M.M.; Rocha, G.A.; et al. Association between pre-sarcopenia, sarcopenia, and bone mineral density in patients with chronic hepatitis C. J. Cachexia Sarcopenia Muscle 2018, 9, 255–268.

29. Sepúlveda-Loyola, W.; Phu, S.; Bani Hassan, E.; Brennan-Olsen, S.L.; Zanker, J.; Vogrin, S.; Santos, N.Q.D.; Nascimento, J.R.A.D., Jr. The Joint Occurrence of Osteoporosis and Sarcopenia (Osteosarcopenia): Definitions and Characteristics. J. Am. Med. Dir. Assoc. 2020, 21, 220–225.

30. Wong, R.M.Y.; Wong, H.; Zhang, N.; Chow, S.K.H.; Chau, W.W.; Wang, J.; Chim, Y.N.; Leung, K.S.; Cheung, W.H. The relationship between sarcopenia and fragility fracture-a systematic review. Osteoporos. Int. 2019, 30, 541–553.

31. Inoue, T.; Maeda, K.; Nagano, A.; Shimizu, A.; Ueshima, J.; Murotani, K.; Sato, K.; Tsubaki, A. Undernutrition, Sarcopenia, and Frailty in Fragility Hip Fracture: Advanced Strategies for Improving Clinical Outcomes. Nutrients 2020, 12, 3743.

32. Goodman, C.A.; Hornberger, T.A.; Robling, A.G. Bone and skeletal muscle: Key players in mechanotransduction and potential overlapping mechanisms. Bone 2015, 80, 24–36.

33. Karasik, D.; Kiel, D.P. Evidence for pleiotropic factors in genetics of the musculoskeletal system. Bone 2010, 46, 1226–1237.

34. Guo, Y.F.; Zhang, L.S.; Liu, Y.J.; Hu, H.G.; Li, J.; Tian, Q.; Yu, P.; Zhang, F.; Yang, T.L.; Guo, Y.; et al. Suggestion of GLYAT gene underlying variation of bone size and body lean mass as revealed by a bivariate genome-wide association study. Hum. Genet. 2013, 132, 189–199.

35. Huang, J.; Hsu, Y.H.; Mo, C.; Abreu, E.; Kiel, D.P.; Bonewald, L.F.; Brotto, M.; Karasik, D. METTL21C is a potential pleiotropic gene for osteoporosis and sarcopenia acting through the modulation of the NF-κB signaling pathway. J. Bone Miner. Res. 2014, 29, 1531–1540.

36. Karasik, D.; Cohen-Zinder, M. The genetic pleiotropy of musculoskeletal aging. Front. Physiol. 2012, 3, 303.

37. Trajanoska, K.; Rivadeneira, F.; Kiel, D.P.; Karasik, D. Genetics of Bone and Muscle Interactions in Humans. Curr. Osteoporos. Rep. 2019, 17, 86–95.

38. Kramer, I.; Baertschi, S.; Halleux, C.; Keller, H.; Kneissel, M. Mef2c deletion in osteocytes results in increased bone mass. J. Bone Miner. Res. 2012, 27, 360–373.

39. Chan, S.; Seto, J.T.; MacArthur, D.G.; Yang, N.; North, K.N.; Head, S.I. A gene for speed: Contractile properties of isolated whole EDL muscle from an alpha-actinin-3 knockout mouse. Am. J. Physiol. Cell. Physiol. 2008, 295, C897–C904.

40. Yang, N.; Schindeler, A.; McDonald, M.M.; Seto, J.T.; Houweling, P.J.; Lek, M.; Hogarth, M.; Morse, A.R.; Raftery, J.M.; Balasuriya, D.; et al. α-Actinin-3 deficiency is associated with reduced bone mass in human and mouse. Bone 2011, 49, 790–798.

41. Kitada, T.; Seki, S.; Iwai, S.; Yamada, T.; Sakaguchi, H.; Wakasa, K. In situ detection of oxidative DNA damage, 8-hydroxydeoxyguanosine, in chronic human liver disease. J. Hepatol. 2001, 35, 613–618.

42. Tilg, H.; Wilmer, A.; Vogel, W.; Herold, M.; Nölchen, B.; Judmaier, G.; Huber, C. Serum levels of cytokines in chronic liver dis eases. Gastroenterology 1992, 103, 264–274.

43. Saito, M.; Marumo, K. Collagen cross-links as a determinant of bone quality: A possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. Osteoporos. Int. 2010, 21, 195–214.

44. Tanaka, K.; Kanazawa, I.; Sugimoto, T. Elevated Serum Pentosidine and Decreased Serum IGF-I Levels are Associated with Loss of Muscle Mass in Postmenopausal Women with Type 2 Diabetes Mellitus. Exp. Clin. Endocrinol. Diabetes 2016, 124, 163–166.

45. Saeki, C.; Saito, M.; Kanai, T.; Nakano, M.; Oikawa, T.; Torisu, Y.; Saruta, M.; Tsubota, A. Plasma pentosidine levels are associated with prevalent fractures in patients with chronic liver disease. PLoS ONE 2021, 16, e0249728.

46. Liu, Z.; Han, T.; Werner, H.; Rosen, C.J.; Schaffler, M.B.; Yakar, S. Reduced Serum IGF-1 Associated with Hepatic Osteodystrophy Is a Main Determinant of Low Cortical but Not Trabecular Bone Mass. J. Bone Miner. Res. 2018, 33, 123–136.

47. George, J.; Ganesh, H.K.; Acharya, S.; Bandgar, T.R.; Shivane, V.; Karvat, A.; Bhatia, S.J.; Shah, S.; Menon, P.S.; Shah, N. Bone mineral density and disorders of mineral metabolism in chronic liver disease. World J. Gastroenterol.

2009, 15, 3516–3522.

48. Retamales, A.; Zuloaga, R.; Valenzuela, C.A.; Gallardo-Escarate, C.; Molina, A.; Valdés, J.A. Insulin-like growth factor-1 suppresses the Myostatin signaling pathway during myogenic differentiation. Biochem. Biophys. Res. Commun. 2015, 464, 596–602.
49. Nishikawa, H.; Enomoto, H.; Ishii, A.; Iwata, Y.; Miyamoto, Y.; Ishii, N.; Yuri, Y.; Hasegawa, K.; Nakano, C.; Nishimura, T.; et al. Elevated serum myostatin level is associated with worse survival in patients with liver cirrhosis. J. Cachexia Sarcopenia Muscle 2017, 8, 915–925.
50. García, P.S.; Cabbabe, A.; Kambadur, R.; Nicholas, G.; Csete, M. Brief-reports: Elevated myostatin levels in patients with liver disease: A potential contributor to skeletal muscle wasting. Anesth. Analg. 2010, 111, 707–709.
51. Cui, Y.; Yi, Q.; Sun, W.; Huang, D.; Zhang, H.; Duan, L.; Shang, H.; Wang, D.; Xiong, J. Molecular basis and therapeutic potential of myostatin on bone formation and metabolism in orthopedic disease. Biofactors 2020. online ahead of print.
52. Puolakkainen, T.; Ma, H.; Kainulainen, H.; Pasternack, A.; Rantalainen, T.; Ritvos, O.; Heikinheimo, K.; Hulmi, J.J.; Kiviranta, R. Treatment with soluble activin type IIB-receptor improves bone mass and strength in a mouse model of Duchenne muscular dystrophy. BMC. Musculoskelet. Disord. 2017, 18, 20.
53. Colaianni, G.; Cinti, S.; Colucci, S.; Grano, M. Irisin and musculoskeletal health. Ann. N. Y. Acad. Sci. 2017, 1402, 5–9.
54. Zhao, M.; Zhou, X.; Yuan, C.; Li, R.; Ma, Y.; Tang, X. Association between serum irisin concentrations and sarcopenia in patients with liver cirrhosis: A cross-sectional study. Sci. Rep. 2020, 10, 16093.
55. Colaianni, G.; Cuscito, C.; Mongelli, T.; Pignataro, P.; Buccoliero, C.; Liu, P.; Lu, P.; Sartini, L.; Di Comite, M.; Mori, G.; et al. The myokine irisin increases cortical bone mass. Proc. Natl. Acad. Sci. USA 2015, 112, 12157–12162.
56. Aydin, S.; Kuloglu, T.; Aydin, S.; Kalayci, M.; Yilmaz, M.; Cakmak, T.; Albayrak, S.; Gungor, S.; Colakoglu, N.; Ozercan, I.H. A comprehensive immunohistochemical examination of the distribution of the fat-burning protein irisin in biological tissues. Peptides 2014, 61, 130–136.
57. Liu, T.Y.; Xiong, X.Q.; Ren, X.S.; Zhao, M.X.; Shi, C.X.; Wang, J.J.; Zhou, Y.B.; Zhang, F.; Han, Y.; Gao, X.Y.; et al. FNDC5 Alleviates Hepatosteatosis by Restoring AMPK/mTOR-Mediated Autophagy, Fatty Acid Oxidation, and Lipogenesis in Mice. Diabetes 2016, 65, 3262–3275.
58. Kitase, Y.; Vallejo, J.A.; Gutheil, W.; Vemula, H.; Jähn, K.; Yi, J.; Zhou, J.; Brotto, M.; Bonewald, L.F. beta-aminoisobutyric Acid, l-BAIBA, Is a Muscle-Derived Osteocyte Survival Factor. Cell. Rep. 2018, 22, 1531–1544.
59. Komori, T. Functions of Osteocalcin in Bone, Pancreas, Testis, and Muscle. Int. J. Mol. Sci. 2020, 21, 7513.
60. Mera, P.; Laue, K.; Wei, J.; Berger, J.M.; Karsenty, G. Osteocalcin is necessary and sufficient to maintain muscle mass in older mice. Mol. Metab. 2016, 5, 1042–1047.
61. Ducy, P.; Desbois, C.; Boyce, B.; Pinero, G.; Story, B.; Dunstan, C.; Smith, E.; Bonadio, J.; Goldstein, S.; Gundberg, C.; et al. Increased bone formation in osteocalcin-deficient mice. Nature 1996, 382, 448–452.
62. Moriishi, T.; Ozasa, R.; Ishimoto, T.; Nakano, T.; Hasegawa, T.; Miyazaki, T.; Liu, W.; Fukuyama, R.; Wang, Y.; Komori, H.; et al. Osteocalcin is necessary for the alignment of apatite crystallites, but not glucose metabolism, testosterone synthesis, or muscle mass. PLoS Genet. 2020, 16, e1008586.
63. Maeda, K.; Kobayashi, Y.; Koide, M.; Uehara, S.; Okamoto, M.; Ishihara, A.; Kayama, T.; Saito, M.; Marumo, K. The Regulation of Bone Metabolism and Disorders by Wnt Signaling. Int. J. Mol. Sci. 2019, 20, 5525.
64. Cisternas, P.; Henriquez, J.P.; Brandan, E.; Inestrosa, N.C. Wnt signaling in skeletal muscle dynamics: Myogenesis, neuromuscular synapse and fibrosis. Mol. Neurobiol. 2014, 49, 574–589.
65. Delgado-Calle, J.; Sato, A.Y.; Bellido, T. Role and mechanism of action of sclerostin in bone. Bone 2017, 96, 29–37.
66. Guañabens, N.; Ruiz-Gaspà, S.; Gifre, L.; Miquel, R.; Peris, P.; Monegal, A.; Dubrueil, M.; Arias, A.; Parés, A. Sclerostin Expression in Bile Ducts of Patients with Chronic Cholestasis May Influence the Bone Disease in Primary Biliary Cirrhosis. J. Bone Miner. Res. 2016, 31, 1725–1733.
67. Kim, J.A.; Roh, E.; Hong, S.H.; Lee, Y.B.; Kim, N.H.; Yoo, H.J.; Seo, J.A.; Kim, N.H.; Kim, S.G.; Baik, S.H.; et al. Association of serum sclerostin levels with low skeletal muscle mass: The Korean Sarcopenic Obesity Study (KSOS). Bone 2019, 128, 115053.
68. Krause, A.; Speacht, T.; Govey, P.; Zhang, Y.; Steiner, J.; Lang, C.; Donahue, H. Sarcopenia and increased body fat in sclerostin deficient mice. J. Bone Miner. Res. 2014, 29, S8–S9.
69. Tang, Y.; Wu, X.; Lei, W.; Pang, L.; Wan, C.; Shi, Z.; Zhao, L.; Nagy, T.R.; Peng, X.; Hu, J.; et al. TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. Nat. Med. 2009, 15, 757–765.

70. Mendias, C.L.; Gumucio, J.P.; Davis, M.E.; Bromley, C.W.; Davis, C.S.; Brooks, S.V. Transforming growth factor-beta induces skeletal muscle atrophy and fibrosis through the induction of atrogin-1 and scleraxis. Muscle Nerve 2012, 45, 55–59.
71. Waning, D.L.; Mohammad, K.S.; Reiken, S.; Xie, W.; Andersson, D.C.; John, S.; Chiechi, A.; Wright, L.E.; Umanskaya, A.; Niewolna, M.; et al. Excess TGF-β mediates muscle weakness associated with bone metastases in mice. Nat. Med. 2015, 21, 1262–1271.
72. Agostini, D.; Zeppa Donati, S.; Lucertini, F.; Annibalini, G.; Gervasi, M.; Ferri Marini, C.; Piccoli, G.; Stocchi, V.; Barbieri, E.; Sestili, P. Muscle and Bone Health in Postmenopausal Women: Role of Protein and Vitamin D Supplementation Combined with Exercise Training. Nutrients 2018, 10, 1103.
73. Wintermeyer, E.; Ihle, C.; Ehnert, S.; Stöckle, U.; Ochs, G.; de Zwart, P.; Flesch, I.; Bahrs, C.; Nussler, A.K. Crucial Role of Vitamin D in the Musculoskeletal System. Nutrients 2016, 8, 319.
74. Garcia, L.A.; King, K.K.; Ferrini, M.G.; Norris, K.C.; Artaza, J.N. 1,25(OH)2vitamin D3 stimulates myogenic differentiation by inhibiting cell proliferation and modulating the expression of promyogenic growth factors and myostatin in C2C12 skeletal muscle cells. Endocrinology 2011, 152, 2976–2986.
75. Girgis, C.M.; Cha, K.M.; Houweling, P.J.; Rao, R.; Mokbel, N.; Lin, M.; Clifton-Bligh, R.J.; Gunton, J.E. Vitamin D Receptor Ablation and Vitamin D Deficiency Result in Reduced Grip Strength, Altered Muscle Fibers, and Increased Myostatin in Mice. Calcif. Tissue Int. 2015, 97, 602–610.
76. Saeki, C.; Kanai, T.; Nakano, M.; Oikawa, T.; Torisu, Y.; Saruta, M.; Tsubota, A. Low Serum 25-Hydroxyvitamin D Levels Are Related to Frailty and Sarcopenia in Patients with Chronic Liver Disease. Nutrients 2020, 12, 3810.
77. Okubo, T.; Atsukawa, M.; Tsubota, A.; Yoshida, Y.; Arai, T.; Iwashita, A.N.; Itokawa, N.; Kondo, C.; Iwakiri, K. Relationship between serum vitamin D level and sarcopenia in chronic liver disease. Hepatol. Res. 2020, 50, 588–597.