

Non-alcoholic fatty liver disease connections with fat-free tissues: A focus on bone and skeletal muscle

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Abstract

The estimates of global incidence and prevalence of non-alcoholic fatty liver disease (NAFLD) are worrisome, due to the parallel burden of obesity and its metabolic complications. Indeed, excess adiposity and insulin resistance represent two of the major risk factors for NAFLD; interestingly, in the last years a growing body of evidence tended to support a novel mechanistic perspective, in which the liver is at the center of a complex interplay involving organs and systems, other than adipose tissue and glucose homeostasis. Bone and the skeletal muscle are fat-free tissues which appeared to be independently associated with NAFLD in several cross-sectional studies. The deterioration of bone mineral density and lean body mass, leading to osteoporosis and sarcopenia, respectively, are age-related processes. The prevalence of NAFLD also increases with age. Beyond physiological aging, the three conditions share some common underlying mechanisms, and their elucidations could be of paramount importance to design more effective treatment strategies for the management of NAFLD. In this review, we provide an overview on epidemiological data as well as on potential contributors to the connections of NAFLD with bone and skeletal muscle.

Key words: Non-alcoholic fatty liver disease; Bone; Skeletal muscle; Osteoporosis; Sarcopenia

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Core tip: Novel epidemiological findings open new avenues for a thorough understanding of the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Liver appears to participate in a fascinating cross-talk with fat-free tissue, mainly bone and skeletal muscle. The identification of contributors other than the classic roles played by excess fat and insulin resistance may

be relevant for the design of more effective treatment strategies for NAFLD.

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INTRODUCTION

In the last decades, a wealth of studies have focused on non-alcoholic fatty liver disease (NAFLD), given that the rising prevalence of this clinical condition has paralleled the obesity epidemic in Western and developing countries^[1,2]. The intrahepatic triglyceride accumulation is the hallmark of NAFLD^[3]; energy imbalance and insulin resistance are considered the most relevant determinants leading to ectopic fat deposition in the liver, and NAFLD has been described as the hepatic manifestation of the metabolic syndrome^[3,4]. Hence, evidence regarding NAFLD is undoubtedly strictly related to excess adiposity and its metabolic consequences^[2-4]. However, in recent years, NAFLD has been associated to diseases and clinical conditions which typically have a natural history that is independent of obesity, such as osteoporosis and the decline of lean body mass, namely sarcopenia^[5,6]. Similar to osteoporosis and sarcopenia, which are notably linked to age-related processes^[7], the prevalence of NAFLD also tends to increase with aging in men and in both premenopausal and postmenopausal women^[8,9]. Furthermore, the association between fatty liver and poor bone mineralization has been also revealed in the pediatric population^[5], expanding the constellation of mechanistic hypotheses other than the known potential contributors characterizing the aging process (e.g., changes in sex steroids)^[8,10]. Therefore, NAFLD appears to be at the center of an intriguing cross-talk involving fat-free tissues, in a new fascinating scenario in which obesity could be only marginally present. In the extant studies, the relationships between NAFLD and bone health, as well as between NAFLD and sarcopenia, have been separately examined. The aim of the present review is to summarize epidemiological evidence and potential underlying mechanisms in the complex interplay among NAFLD, bone, and skeletal muscle. Relevant peer-reviewed journal articles published in English were identified in the MEDLINE database (the last search was conducted on August 31, 2016); different combinations of the following search terms were used: "nonalcoholic fatty liver disease", "bone", "skeletal muscle mass", "lean body mass".

Also the following exclusion criteria were used:

any paper dealing with viral or autoimmune hepatic disease, inherited metabolic disorders, excessive alcohol intake; any paper including the definition of NAFLD based on clinical chemistry data only (e.g., elevated aminotransferase levels); any paper on sarcopenia associated to cancer cachexia or neurological diseases, inflammatory or autoimmune diseases, corticosteroids for systemic use; any paper including bedridden subjects; any paper concerning osteoporosis as secondary disease; any paper in which fractures and not bone mineral density (BMD), were the main outcome; any paper evaluating markers of bone turnover without data on BMD; and any study conducted in animals. Review articles and secondary data analyses, letters in response to published articles, editorials, commentaries and conference abstracts were excluded.

NAFLD AND BONE MINERAL DENSITY

Most studies dealing with BMD in subjects with fatty liver were conducted in the Asian population, and liver ultrasonography was the most used method for the diagnosis of NAFLD. BMD was assessed by dual energy X-ray absorptiometry (DXA) in all studies, but different sites of the skeleton, or whole body BMD, were examined (Table 1)^[11-22]. The association between NAFLD and decreased BMD has been reported in both genders, and also confirmed in children and adolescents, in the majority of the studies, with few exceptions^[13,16,20].

Xia *et al.*^[11] reported a negative association between NAFLD and any site of the skeleton examined in Chinese men and postmenopausal women aged 46-93 years. Similarly, Cui *et al.*^[12] described a negative association between NAFLD and BMD (as average of BMD at the femoral neck, hip, and lumbar spine) in Chinese men and postmenopausal women (aged 40-70 years). However, both genders with NAFLD showed lower BMD at the hip than controls, whereas no difference was found at the lumbar level. In a large Korean cohort including men aged 40 years and older, and postmenopausal women, Lee *et al.*^[13] observed a negative association between NAFLD and the femoral neck BMD in men, whereas a positive relationship emerged between NAFLD and lumbar spine BMD in women. Moon *et al.*^[14] reported that a negative association between NAFLD and lumbar spine BMD was present in postmenopausal, but not premenopausal women. However, in these studies liver ultrasound was used to diagnose NAFLD. It is well known that sonography is highly operator-dependent, and has limited repeatability and reproducibility because it evaluates liver fat content on the basis of subjective qualitative features of liver echogenicity^[23]. In addition, just a few studies examined thoroughly multiple sites or whole body bone mineral density. Bhatt and coll. assessed BMD in different skeletal segments, and surprisingly, found higher BMD values

Table 1 Studies exploring the association between non-alcoholic fatty liver disease and bone mineral density

Ref.	Study population and sample size	Race/ethnicity	NAFLD assessment	Skeleton: segments	Main findings: BMD
Xia <i>et al</i> ^[11] , 2016	Elderly men (<i>n</i> = 755) and postmenopausal women (<i>n</i> = 904) divided into quartiles of liver fat content (LFC)	Chinese	Liver quantitative US	Lumbar spine, hip, whole body	BMD in any skeletal segment was lower in the highest LFC quartile compared to the lowest quartile. LFC inversely correlated with BMD (all skeletal segments)
Cui <i>et al</i> ^[12] , 2013	Men with NAFLD (<i>n</i> = 46) vs male controls (<i>n</i> = 53); postmenopausal women with NAFLD (<i>n</i> = 73) vs female controls (<i>n</i> = 52)	Chinese	Liver US	Lumbar spine, right hip, femoral neck	Lower BMD at the right hip in participants with NAFLD than controls (in both genders); lower BMD at the femoral neck in men with NAFLD vs controls. Negative association between NAFLD and BMD
Lee <i>et al</i> ^[13] , 2016	Men with NAFLD (<i>n</i> = 1288) vs male controls (<i>n</i> = 2018); postmenopausal women with NAFLD (<i>n</i> = 1217) vs female controls (<i>n</i> = 2112)	Korean	Liver US	Lumbar spine and femoral neck	Negative association between femoral neck BMD and NAFLD in men; positive correlation between lumbar spine BMD and NAFLD in postmenopausal women
Moon <i>et al</i> ^[14] , 2012	Premenopausal women with NAFLD (<i>n</i> = 162) vs controls (<i>n</i> = 54), and postmenopausal with NAFLD (<i>n</i> = 102) vs controls (<i>n</i> = 163)	Korean	Liver US	Lumbar spine	Higher BMD in the control group than postmenopausal women NAFLD; NAFLD negatively associated with BMD in postmenopausal women, but not premenopausal women
Purnak <i>et al</i> ^[15] , 2012	Men (<i>n</i> = 52) and women (<i>n</i> = 50) with NAFLD vs healthy men (<i>n</i> = 28) and women (<i>n</i> = 26)	Caucasian	Liver US	Femur (neck, trochanter, intertrochanteric region and total femur) and lumbar spine	Lower lumbar spine and femoral neck BMD Z-scores in women with high ALT levels
Bhatt <i>et al</i> ^[16] , 2013	Men (<i>n</i> = 129) and women (<i>n</i> = 33) with NAFLD vs controls (men, <i>n</i> = 109; women, <i>n</i> = 64)	Indian	Liver US	Trunk, pelvis, spine, whole body	Higher BMD values in NAFLD subjects than controls
Yang <i>et al</i> ^[17] , 2016	Men with NAFLD (<i>n</i> = 249) vs male controls (<i>n</i> = 610)	Korean	Liver US	Right Hip	NAFLD negatively associated with right-hip BMD
Pacifico <i>et al</i> ^[18] , 2013	Obese children with NAFLD (boys, <i>n</i> = 24, and girls, <i>n</i> = 20) vs obese controls (boys, <i>n</i> = 24, and girls, <i>n</i> = 20)	Caucasian	MRI + liver biopsy	Lumbar spine and whole body	Lower lumbar BMD Z-score in NAFLD children than controls. Negative association of lumbar BMD and whole-body BMD Z-scores with NASH
Pardee <i>et al</i> ^[19] , 2012	Obese children (10-17 yr) with (<i>n</i> = 38) or without (<i>n</i> = 38) NAFLD	Mixed (89.5% Hispanic, 10.5% non-Hispanic, White)	Liver biopsy	Whole body	Lower whole body BMD Z-score in children with NAFLD than children without NAFLD. Lower whole body BMD Z-score in children with NASH than children without NASH
Chang <i>et al</i> ^[20] , 2015	Obese children and adolescents with NAFLD (<i>n</i> = 15) vs obese children and adolescents with NASH (<i>n</i> = 47) vs controls (<i>n</i> = 32)	Korean	Liver US (NAFLD); liver US + elevated serum aminotransferase levels (NASH)	Arm, leg, trunk, whole body	Age-matched BMD Z-scores were not different between groups
Pirgon <i>et al</i> ^[21] , 2011	Obese children with NAFLD (boys, <i>n</i> = 19, and girls, <i>n</i> = 23) vs obese children (boys, <i>n</i> = 18, and girls, <i>n</i> = 22) and lean children (boys, <i>n</i> = 15, and girls, <i>n</i> = 15)	Caucasian (Turkish)	Liver US	Lumbar spine	Lower lumbar BMD-SDS in obese adolescents with NAFLD compared with obese and lean adolescents without NAFLD
Campos <i>et al</i> ^[22] , 2012	Obese adolescents with NAFLD (<i>n</i> = 18) vs obese adolescents without NAFLD (<i>n</i> = 22)	Brazilian	Liver US	Whole body	Obese adolescents with NAFLD had a significantly lower values of BMC than their counterparts without NAFLD. No differences in BMD Z-scores

BMC: Bone mineral content; BMD-SDS: Bone mineral density-standard deviation score; BMD: Bone mineral density; LFC: Liver fat content; MRI: Magnetic resonance imaging; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; US: Ultrasound; ALT: Alanine aminotransferase.

in some bone sites (namely, trunk, pelvis, spine, and also whole body BMD) in adult subjects with NAFLD compared to controls^[16]. In this study, participants with NAFLD had a higher BMI and a higher body fat than controls, and any adjustments for either BMI or body fat were not considered in the comparison of BMD between groups: this may account for the discrepant results obtained^[16]. Currently it is unclear

if the presence of NAFLD is associated to a higher susceptibility to bone mass deterioration in any specific segment of the skeleton, and this research question, together with a more in-depth investigation of gender differences, needs to be addressed in future studies. However, evidence from pediatric studies, in which NAFLD was biopsy-proven, suggests that the effects of the interrelationship between fatty liver and bone is

already present in the first decades of life, and whole body bone mass seems to be affected^[18,19]. Pacifico *et al.*^[18] evaluated lumbar spine BMD and whole body BMD in obese children with fatty infiltration of the liver, as assessed through MRI (two-point Dixon method) and liver biopsy. Compared to controls, children with NAFLD had lower whole body BMD and lumbar spine BMD; similarly, whole body BMD Z-score and lumbar segmental BMD Z-score were significantly lower according to histological staging. The association between NAFLD and BMD was maintained even after adjustment for fat mass or high-sensitivity C-reactive protein levels. Conversely, Chang *et al.*^[20] described no difference in age-matched BMD Z-scores in Korean children with simple steatosis or NASH, compared to controls; in that study, the diagnosis of NAFLD was based on liver ultrasonography, and NASH was defined as the presence of elevated transaminase levels in children with NAFLD. These observations need to be consolidated by further research in larger cohorts, using gold-standard methods for the evaluation of fatty liver.

NAFLD AND SKELETAL MUSCLE

Growing interest has been directed to the involvement of skeletal muscle mass in chronic liver disease, especially in cirrhosis. The decline in lean body mass, namely sarcopenia, has been recognized as one of the comorbidities accompanying liver cirrhosis, likely related to malnutrition occurring in cirrhotic patients^[24]. Beyond chronic liver disease of viral or auto-immune origin, several studies have described the phenotype of sarcopenia in subjects with NAFLD (Table 2)^[25-31]. Evidence concerning the deterioration of skeletal muscle in NAFLD is scarce, and data from pediatric studies are lacking, due to several reasons. First, sarcopenia is an age-related process, with prevalence increasing in late life^[7]. However, the coexistence of risk factors such as obesity and physical inactivity may be responsible for a more precocious onset of this clinical condition. Second, contrary to osteoporosis and reduction of the BMD in the pregeriatric population, universally accepted criteria for the diagnosis of sarcopenia are lacking and are still under debate^[32]. In the extant studies investigating the relationship between sarcopenia and NAFLD, the skeletal muscle mass was assessed by DXA or bioimpedance analysis (BIA), and different indices of sarcopenia were used. The majority of studies relied on the use of surrogate indices to identify NAFLD and fibrosis in NAFLD. Moreover, the Asian population has been mainly investigated, whereas evidence from other ethnic groups is scarce to date. In the Korean Sarcopenic Obesity Study, Hong *et al.*^[6] demonstrated that participants in the lowest skeletal muscle index quartile exhibited a higher odds ratio of having NAFLD (defined by the liver attenuation index from abdominal computed tomography) than subjects in

the higher quartiles. Interestingly, this association was maintained even after adjustment for potential confounders such as age, sex, physical activity level, homeostasis model assessment of insulin resistance (HOMA-IR), C-reactive protein, and vitamin D levels. In a different cohort of Korean subjects with a biopsy-proven diagnosis of NAFLD, Koo *et al.*^[25] found that the prevalence of sarcopenia [defined by the appendicular skeletal muscle mass divided by body weight or normalized to body mass index (BMI)], increased according to NAFLD histological grades (steatosis and ballooning) and fibrosis stage. In addition, the odds ratio of having NASH was increased in sarcopenic subjects compared to their nonsarcopenic counterparts, independent of obesity and HOMA-IR. In the remaining studies, the assessment of NAFLD or liver fibrosis was based on the calculation of surrogate indices (Table 2). In a large population-based study, namely the KHANES 2008-2011, Lee *et al.*^[26] observed an approximately two-fold higher risk of liver fibrosis in sarcopenic subjects with NAFLD, independent of obesity and insulin resistance. Analogous observations were provided by other studies carried out in Korean, Japanese and Italian cohorts^[27-31], showing that the relationship linking NAFLD and sarcopenia was independent of the classic risk factors such as obesity, insulin resistance or other metabolic covariates. Notably, the aforementioned studies included mainly middle-aged and elderly participants. As such, the reciprocal influence of NAFLD and skeletal muscle in the first decades of life remains to be clarified.

POTENTIAL MECHANISMS UNDERLYING THE INTERPLAY BETWEEN NAFLD, BONE, AND SKELETAL MUSCLE

Growth hormone/insulin-like growth factor 1 axis

The growth hormone/insulin-like growth factor 1 (GH/IGF1) axis is involved in protein metabolism in the skeletal muscle as well as bone growth and remodeling^[33,34]. The age-related decline of the somatotrophic axis activity, namely the somatopause, represents an important determinant of the development of osteoporosis and sarcopenia^[34]. Recent evidence highlights the crucial role of IGF1 signaling in the cross-talk linking striated muscle and bone^[35]. Furthermore, NAFLD is a frequent comorbidity observed in patients with GH deficiency, with a more rapid progression to NASH^[36]. Several studies have also reported decreased levels of IGF1, that is the major mediator of GH action, in subjects with NAFLD^[37]. GH and IGF1 influence carbohydrate and lipid metabolism, with opposite actions: IGF1 stimulates glucose uptake, favoring insulin signaling, whereas GH induces lipolysis, determining insulin resistance mediated by elevated free fatty acid levels^[38,39]. However, the association between NAFLD and IGF1 appears to be independent of insulin resistance^[40]. Sumida *et al.*^[41]

Table 2 Studies exploring the association between non-alcoholic fatty liver disease and skeletal muscle mass

Ref.	Study population and sample size	Race/ethnicity	NAFLD assessment	Skeletal muscle mass assessment	Main findings: skeletal muscle
Hong <i>et al</i> ^[6] , 2014	Men (<i>n</i> = 32) and women (<i>n</i> = 96) with sarcopenia <i>vs</i> men (<i>n</i> = 135) and women (<i>n</i> = 189) without sarcopenia	Korean	LAI	DXA: -SMI = SMM/weight (%)	Increased ORs of NAFLD in individuals with SMI value in the lower quartiles
Koo <i>et al</i> ^[25] , 2016	Adults with NAFLD (<i>n</i> = 117) <i>vs</i> adults with NASH (<i>n</i> = 123) <i>vs</i> controls (<i>n</i> = 69)	Korean	Liver biopsy, Fibroscan	BIA: -ASM (kg) -ASM/weight (%) -ASM/BMI	Lower ASM (%) and ASM/BMI in NAFLD and NASH than controls; higher prevalence of sarcopenia in NAFLD and NASH groups than control group
Lee <i>et al</i> ^[26] , 2015	Men (<i>n</i> = 5617) and women (<i>n</i> = 9515) divided into four groups: sarcopenic obese (<i>n</i> = 2455) <i>vs</i> non-sarcopenic obese subjects (<i>n</i> = 2198); sarcopenic non-obese (<i>n</i> = 2004) <i>vs</i> non-sarcopenic non-obese subjects (<i>n</i> = 8475)	Korean	For NAFLD: HSI, CNS For fibrosis: BARD, FIB-4	DXA: -ASMI = ASM/weight (%)	Inverse correlation between all indices of NAFLD and SMI Increased ORs of NAFLD and advanced fibrosis in subjects with sarcopenia
Hashimoto <i>et al</i> ^[27] , 2016	Diabetic men with NAFLD (<i>n</i> = 58) <i>vs</i> controls (<i>n</i> = 21), and diabetic women with NAFLD (<i>n</i> = 39) <i>vs</i> controls (<i>n</i> = 27)	Japanese	CAP FIB-4	BIA: -SMM (kg) -SMI = SMM/weight (%)	Negative association between CAP and SMI in men; no significant association in women
Moon <i>et al</i> ^[28] , 2013	Low FLI group (men = 1641, and women, <i>n</i> = 1180) <i>vs</i> intermediate FLI group (men, <i>n</i> = 2600, and women, <i>n</i> = 2296) <i>vs</i> high FLI group (men, <i>n</i> = 1052, and women, <i>n</i> = 796)	Korean	FLI	BIA: -SMI = SMM/weight (%) -SVR = SMM/VFA	Lower SMI in the high FLI group and the intermediate FLI group than the low FLI group. Negative correlation between FLI and SMI, and between FLI and SVR. The highest SVR quartile had a lower OR for FLI \geq 60
Kim <i>et al</i> ^[29] , 2016	FLI \geq 60 group (men, <i>n</i> = 208, and women, <i>n</i> = 181) <i>vs</i> FLI < 60 group (men, <i>n</i> = 976, and women, <i>n</i> = 2374)	Korean	FLI	DXA: -ASM (kg) -SMI = ASM/weight (%)	Lower SMI in the high FLI group than the low FLI group in both genders. Increased ORs for FLI-defined NAFLD in men and women with low SMI
Lee <i>et al</i> ^[30] , 2016	Men (<i>n</i> = 1241) and women (<i>n</i> = 1520) with NFSL-based NAFLD divided into two groups: sarcopenic subjects (<i>n</i> = 337) <i>v.</i> non-sarcopenic subjects (<i>n</i> = 2424)	Korean	For NAFLD: NLFS, CNS, HSI; For fibrosis: NFS, FIB-4, Forns index	DXA: -SI = ASM/BMI	Higher NFS, FIB-4, and Forns index in the sarcopenic group than the non-sarcopenic group; negative association of SI with NFS, FIB-4, and Forns index
Poggiogalle <i>et al</i> ^[31] , 2016	Obese men (<i>n</i> = 81) and women (<i>n</i> = 346) divided into 2 groups: FLI 20 \leq FLI < 60 (<i>n</i> = 61) and FLI \geq 60 (<i>n</i> = 359) (FLI \leq 20 in 7 subjects only, excluded from the analysis)	Caucasian (Italian)	FLI	DXA: -TrFM/ASM ratio	Positive association between FLI and TrFM/ASM ratio (indicating high visceral adiposity and low appendicular muscularity)

ASM: Appendicular skeletal mass; ASMI: Appendicular skeletal mass index; BMI: Body mass index; CAP: Controlled attenuation parameter; CNS: Comprehensive NAFLD score; CT: Computed tomography; FLI: Fatty liver index; HIS: Hepatic steatosis index; LAI: Liver attenuation index; NAFLD: Non-alcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; NFS: NAFLD fibrosis score; SI: Sarcopenia index; NLFS: NAFLD liver fat score; SMI: Skeletal muscle index; SMM: Skeletal muscle mass; SVR: Skeletal muscle to visceral fat ratio; TrFM: Truncal fat mass; VFA: Visceral fat area.

found that IGF1 levels and IGF1-standard deviation score (SDS) values were lower in Japanese subjects with NAFLD at the histological examination when compared to controls; moreover, IGF1-SDS values were associated with the histological severity of NAFLD, independent of insulin resistance. Similarly, in a large population-based study, Völzke *et al*^[42] described an association between low IGF1 and IGF1/IGFBP3 ratio and liver hyperechogenicity, independent of BMI and diabetes. Though the prevalence of hepatic steatosis, and the deterioration of lean body mass and BMD tend to increase with age^[7,8], paralleling the somatopause, the GH/IGF1 axis affects the liver, the skeletal muscle and bone health even in earlier stages of life. In fact, IGF1 is known to stimulate longitudinal bone growth^[43], and recently an analogous action has been attributed also to GH, independent of IGF1^[44]. A robust correlation between IGF1 levels and bone mass has been shown to occur in early pubertal stages in

both genders^[45]. Cianfarani *et al*^[46] found that IGF1 levels were associated with NAFLD activity score and histological patterns in obese children with biopsy-proven NAFLD. A recent study by Cabrera and coll. shed light on the underlying mechanisms linking IGF1, NAFLD and sarcopenia^[47]. In mice NAFLD was induced by an American Lifestyle-Induced Obesity Syndrome (ALIOS) diet model, based on a Western dietary pattern combined to fructose excess. Muscle fiber size and muscle strength, as well as IGF1 levels decreased in animals with diet-induced NAFLD. Interestingly, the phenotypic aspects of sarcopenia were observed prior to the development of liver fibrosis, indicating that they could occur in early stages of NAFLD natural history^[47].

Vitamin D deficiency

Vitamin D deficiency has been postulated to play a role in the pathogenesis of NAFLD. Two recent quantitative

meta-analysis (including twenty-three and nine studies, respectively) concluded that 25(OH)D levels were lower in subjects with NAFLD or NASH than in individuals without fatty liver^[48,49]. If cross-sectional studies support the potential influence of vitamin D status on NAFLD^[50], limited evidence exists proving the effectiveness of vitamin D supplementation in NAFLD patients^[51,52]. However, findings from animal models revealed that vitamin D interferes with the activation of hepatic stellate cell, which are responsible for collagen deposition and extracellular matrix remodeling, leading to fibrosis^[53]. Vitamin D seems to inhibit hepatic stellate cell proliferation^[53], and clinical trials are needed to demonstrate that vitamin D supplementation could slow down the progression from NAFLD to NASH. Vitamin D is well known to exert pleiotropic effects. Vitamin D plays a relevant role in bone homeostasis: vitamin D deficiency determines secondary hyperparathyroidism and accelerated bone turnover^[54]. Inadequate vitamin D levels have been reported in subjects with osteoporosis, even if only modest beneficial effects of vitamin D supplementation have been shown in fracture prevention^[55]. In the last years mounting interest has been addressed to vitamin D action in skeletal muscle. Reduced vitamin D levels have been associated with sarcopenia, disability, and falls in the elderly^[56,57]. In adults with vitamin D deficiency, histological alterations in muscle fiber composition and diameter have been described^[58]. In disagreement with the above mentioned data, among the studies included in the present review, Hong *et al*^[6] found no significant association between 25(OH)D levels and skeletal muscle index or liver attenuation index in Korean men and women. Methodological issues exist in the studies which explored vitamin D status, especially related to seasonality, variability in sun exposure, coexistence of obesity and physical inactivity. The presence of these potential confounders limits the interpretation of the available data.

Osteocalcin

Osteocalcin is a bone-derived hormone, mainly produced by the osteoblasts, and is a non-collagenous matrix protein. Osteocalcin is considered as a serum biomarker of bone formation. In a number of studies a negative association has been described between serum osteocalcin levels and decreased bone mineral density in postmenopausal women^[59,60]. Emerging evidence from animal and human studies unveiled that osteocalcin is involved in many homeostatic mechanisms other than those specific for bone health^[61,62]. Notably, osteocalcin is able to interfere with energy and glucose metabolism, modulating pancreatic beta-cell activity. Undercarboxylated osteocalcin is the active isoform of the hormone, responsible for inducing insulin secretion and favoring insulin sensitivity in skeletal muscle and adipose tissue^[61,62]. Accumulating evidence suggests that osteocalcin is also involved in

liver disease; low serum osteocalcin levels have been related to NAFLD. In a case-control study, Yilmaz and coworkers found that osteocalcin was inversely associated with histological features of NAFLD^[63]. Moreover, this inverse association linking osteocalcin and NAFLD has been also reported in male and female participants with normal bone mineral density^[64-66]. In an experimental model of diet-induced NAFLD, the administration of osteocalcin was demonstrated to be effective in reversing metabolic changes and reducing markedly hepatic triglyceride content, suggesting a protective role of osteocalcin in NAFLD development^[67]. Interestingly, osteocalcin has been shown to play a crucial role also in the inter-organ cross-talk between the skeleton and skeletal muscle. Osteocalcin signaling in myofibers seems to be an important mediator of metabolic adaptive mechanisms to exercise^[68]. In addition, recently Mera and coll. showed that in mice exogenous osteocalcin administration promoted protein synthesis in myotubes, preventing the age-related muscle loss^[69]. Further evidence is required to establish if osteocalcin may represent a suitable candidate for counteracting muscle wasting and liver fat infiltration.

Insulin resistance

NAFLD is known to be the hepatic manifestation of the metabolic syndrome, due to the remarkable effects of insulin resistance in the pathogenesis of hepatic steatosis^[70]. Intrahepatic lipid accumulation has been related to the deterioration of insulin sensitivity at the level of liver, skeletal muscle, and adipose tissue^[71]. Furthermore, the presence of NAFLD predicts the risk of developing type 2 diabetes, independent of age and obesity^[72]. Furthermore, insulin resistance is a key factor also in anabolic processes taking place in the skeletal muscle and bone. The skeletal muscle is the major target tissue of insulin action^[73]. On one hand, insulin resistance interferes with the effectiveness of protein synthesis, leading to the age-related reduction of lean body mass^[74]. In nondiabetic elderly subjects, Guillet *et al*^[75] reported that insulin ability to counteract whole body protein break down was decreased. On the other hand, the presence of reduced lean mass can further favor the development of insulin resistance^[74]. In vitro and in vivo studies demonstrated that insulin plays an important role in bone homeostasis. Insulin promotes osteoblast proliferation and differentiation, the generation of anabolic signals and collagen synthesis, influencing microarchitecture and mechanical properties of bone^[76]. A complex connection exists between bone metabolism and insulin resistance, with the frequent overlap of insulin resistance and excess adiposity being the major confounding factor. Due to the increased mechanical load on the skeleton, obesity appeared to confer protection against bone mass deterioration. In addition, bone turnover seemed to

be lower in subjects with the metabolic syndrome and type 2 diabetes^[77]. Even if evidence is not conclusive, especially for the prevention of fragility fractures^[78], this assumption has been weakened by a number of studies in which the relationship between metabolic syndrome and bone outcomes, such as bone strength or areal BMD, became negative in models adjusted for BMI^[79]. In fact, several studies reported a negative association between insulin resistance and bone mineral density as well as bone strength indices and markers of bone formation^[80-82]. Novel findings from animal studies unveiled that bone represents a site of insulin resistance, and osteoblasts are primarily involved in insulin signaling in bone. In more detail, in mice fed a high-fat diet, insulin resistance in osteoblasts was responsible for the reduced production of osteocalcin, which in turn affected detrimentally whole body insulin sensitivity^[83,84]. Furthermore, in a model of high-fat diet induced obesity in rats, the development of insulin resistance led to reduced osteoblast proliferation and differentiation, and increased osteoblast apoptosis, resulting in decreased jaw bone density^[85].

Chronic inflammation

A proinflammatory milieu represents another common soil favoring the development of the three conditions examined in the present review. Systemic inflammation is one of the major actors in the progression from NAFLD to NASH^[86]. Liver resident cells, like hepatic stellate cells, Kupffer cells, and dendritic cells, generate pro-inflammatory signals involved in the cascade leading to cell death^[86]. In addition, tumor necrosis factor- α (TNF- α) is another relevant mediator and inducer of hepatocyte death^[87]. Also in aged skeletal muscle, TNF- α signaling is involved in the activation of apoptosis, leading to muscle fiber loss and sarcopenia^[88]. Though the role of proinflammatory cytokines, IL-6, in protein breakdown in skeletal muscle is controversial^[89,90], epidemiological evidence underpins the relationship between chronic low-grade inflammation and age-related sarcopenia^[91]. The interplay between TNF- α and the RANKL/RANK/osteoprotegerin system is crucial for the modulation of osteoclast activity and bone resorption and remodeling^[92]. Recently, reduced osteoprotegerin levels have been described in NAFLD, independent of potential confounders^[93,94]. Taken together, these observations emphasize the connections linking immune response, inflammation, and bone physiology to NAFLD.

Physical inactivity

Sedentariness is a well-known risk factor for weight gain and the consequences related to excess fat, including the onset of fatty liver^[95]. Indeed, lifestyle interventions, combining dietary interventions and physical activity, have been demonstrated to be beneficial in terms of liver fat reduction, due to weight

loss. Interestingly, mounting evidence supports an exercise effect and a physical fitness role *per se* in the pathophysiology of NAFLD^[96]. In fact, based on pooled data from six studies, a recent meta-analysis revealed that exercise alone (vs non-exercise control, without any dietary intervention) was sufficient to determine a significant decrease of the intrahepatic lipid content, even in the absence of weight change, or minimal weight loss^[97].

Physical inactivity represents also a well-established risk factor for both sarcopenia and osteoporosis. The lack of physical activity favors the decline of lean body mass, triggering a vicious cycle leading to both progressive inactivity and sarcopenia^[98]. Similarly, physical activity is recognized as a relevant factor in promoting bone health across the lifespan^[99,100]. According to the mechanostat theory, bone and skeletal muscle are connected by mechanical interactions. In the last years, skeletal muscle and bone have been demonstrated to act as endocrine organs, producing several factors responsible for this intriguing inter-organ cross-talk^[101].

Among a number of factors involved in the above mentioned interplay, irisin is a recently described hormone-like myokine. Plasma irisin levels increase in response to exercise; moreover, irisin is able to increase energy expenditure. Irisin autocrinally modulates some metabolic functions in the skeletal muscle, and it also exerts endocrine effects on adipocytes and osteoblasts. In fact irisin can induce browning of white adipose tissue, and can regulate the expression of osteogenic genes as well as it is able to induce differentiation of osteoblasts^[102]. Zhang *et al.*^[103] reported that circulating irisin was negatively associated with intrahepatic triglyceride content in Chinese obese adults with NAFLD, independent of other metabolic factors. Due to the pleiotropic effects on energy metabolism, glucose homeostasis, insulin resistance, and obesity, irisin may represent a pivotal mediator in the complex communication among the liver, skeletal muscle and bone^[104,105].

CONCLUSION

Emerging evidence supports the crucial role played by new contributors in the pathogenesis of NAFLD in a complex inter-organ communication, widening the classic paradigm centered on insulin resistance and excess fat. In this emerging perspective, fat-free tissues like bone and skeletal muscle appear to be relevant actors. Though the novel findings are fascinating, the roles of fat-free tissues, independent of obesity and classic risk factors for NAFLD, need to be further investigated. More rigorous methods for the diagnosis of NAFLD and sarcopenia should be used. The extant evidence needs to be confirmed in different races and ethnicities, and further research should be prompted in order to narrow the gap in the literature, especially with regard to the connection between

NAFLD and skeletal muscle in the early stages of the aging process.

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