**Recent advances in the association between osteoporotic fracture and sarcopenia**

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**Abstract:**The risk of osteoporotic fracture can be viewed as a function of loading conditions and the ability of the bone to withstand the load. Skeletal loads are dominated by muscle action. Recently, it has become clear that bone and muscle share genetic determinants. Involution of the musculoskeletal system manifests as bone loss (osteoporosis) and muscle wasting (sarcopenia). There are clinical evidences that osteoporotic fractures are significantly positively related to sarcopenia, sarcopenia may be a potential predictive value for fracture risk,which suggested that there may be the share gentic determinants between sarcopenia and osteoporotic fracture.In recent years, GWAS studies have found that both lean mass and hand grip strength are associated with fracture risk , which may provide a possible endophenotype for elucidating the potential genetic study of fracture risk.Our effort to understand the clinical and genetic correlation between osteoporotic fracture and sarcopenia is helpful to understand the interaction between muscle and bone, and to study the etiology of complex musculoskeletal diseases, so as to create a drug / intervention method for osteoportic fracure in the future.Identification of potentially important genetic variations in bone and muscle, measurement with state-of-the-art technology, and replication experiments in large humans and animals will provide valuable potential targets for osteoporotic fracture and pharmacogenetic applications for important research.

Keywords: genetics, osteoporotic, fracture, sarcopenia,genome-wide association studies, single
nucleotide polymorphism

**~~Disease definitions and overview~~ Introduction**

Osteoporosis (OP) is a systemic skeletal disorder characterized by reduced bone mass and strength, increased risk of fractureb with aging[1]. It is a major public health problem. At present, more than 200 million people worldwide suffer from osteoporosis. Among the population over the age of 50, bone loss leads to a rapid increase in fracture risk and mortality in the elderly, and one in five men or three women may suffer from osteoporotic fracture [2]. The most serious harm of OP is the occurrence of fragility fracture, with a predominance of hip, vertebrae and distal radius fracture, resulting in huge social and economic burdens.

Sarcopenia (SP) is defined as the progressive loss of muscle mass and/or muscle function with aging,leading to increased risk of falls and fractures [3]. It is estimated that about 50 million people worldwide suffer from sarcopenia, and the number is expected to reach 500 million by 2050. The co-emergence of sarcopenia and osteoporosis was considered components of “dysmobility syndrome”, which makes the elderly prone to falls and fractures and has become the main cause of disability and death in the elderly [4]. With the aging global population, the musculoskeletal disorder accounts for approximately 7.5% of elderly diseases [5], which has become an important public health problem. Prospective clinical studies in several countries have shown that patients with hip fractures were complicated with sarcopenia of varying degrees [6], which has proved that sarcopenia is an important risk for osteoporotic fracture.

The risk of osteoporotic fracture can be viewed as a function of loading conditions and the ability of the bone to withstand the load. Skeletal loads are dominated by muscle action. Recently, it has become clear that bone and muscle share genetic determinants. Involution of the musculoskeletal system manifests as bone loss (osteoporosis) and muscle wasting (sarcopenia). Previous studies have found that bone and muscle tissue are closely related, and both are not only positionally adjacent and biomechanically interrelated, but also connected with tissue metabolism, genetics, endocrine factors, chronic inflammation, malnutrition, exercise and other systemic factors which collectively regulate skeletal and muscle activity. Since osteoblasts and myoblasts are derived from bone marrow mesenchymal stem cells, bone and muscle may be regulated by some of the same genetic factors. Sarcopenia and osteoporosis are both biologically and functionally associated with an increased risk of fracture in the elderly. Patients with sarcopenia and osteoporosis are due to decreased muscle mass and strength, bone density and mobility, and increased risk of falls and osteoporotic fractures [7], resulting in decreased quality of life and increased mortality in the elderly.

**Clinical evidence ~~between~~ for an association between osteoporotic fractures and sarcopenia ~~Sarcopenia is closely associated with osteoporosis, which increases the risk of fracture together.~~**

Most large cross-sectional studies showed that bone mineral density (BMD) was positively correlated with muscle mass, and decreased muscle mass was an important risk for osteoporotic fractures. A study of 17,891 cases including African Americans, Caucasians, and Chinese, ~~which were~~ showed that muscle mass and grip strength were positively correlated with BMD ~~bone mineral density~~, with the risk of bone mass loss/osteoporosis decreased by 37% for every 1 standard deviation increase in appendicular lean mass. Compared to normal individuals, the risk of osteopenia/osteoporosis was ~~is~~ 1.8 times higher in patients with sarcopenia [8]. More than 3,400 men and women over 60 years old were included in the South Korean Health and Nutrition Survey. Skeletal muscle content, bone mineral density and serum 25 hydroxyvitamin D levels were measured, and the survey showed that sarcopenia combined with vitamin D deficiency group had significantly lower bone mineral density of total hip and femoral neck in both men and women [9]. A study in Shanghai of China, which enrolled 1766 men and 1778 women aged 18-96 years, showed that the prevalence of sarcopenia was 4.8% in women and 13.2% in men over 70 years old, which was close to the prevalence in Japan and South Korea and lower than in Caucasians. Participants' lower limbs and trunk muscle mass were strong predictors of femoral and spine BMD, respectively [10].

Sarcopenia is not only strongly associated with low bone density, but also an important risk for hip fracture. Finnish studies in the association between sarcopenia and osteoporosis in postmenopausal women divided 590 cases into 4 groups, sarcopenia, sarcopenia, nonsarcopenia, and unclassified, showed that sarcopenic women had significantly higher risks of osteoporosis, fractures, and at least 1 fall in 1 year compared with nonsarcopenic women, with odds ratios of 12.9, 2.7, and 2.1, respectively [11]. A cross-sectional Italian study of 591 male and female patients admitted to a rehabilitation facility for hip fracture, using the limb muscle index to diagnose sarcopenia, revealed that 116 (21.8%) females and 52 (86.7%) males had sarcopenia [12]. A Japanese cross-sectional study by HIDA et al., which enrolled 2868 healthy institutions of both genders, 357 had previously suffered hip fracture, and the proportion of patients with sarcopenia and lower limb muscle index reduction in the fracture group was significantly higher than that in the non fracture group, indicating that aging, low BMD, and sarcopenia are the major risk factors for hip fracture [13]. Thus, sarcopenia is not only closely related to low bone density, but also an important risk factor for falls and fractures.

~~Although~~ There are ~~some~~ studies that ~~did~~ have not ~~find~~ found any association between sarcopenia, osteoporosis, and fractures, which may be related to different diagnostic methods of sarcopenia, ethnic and regional differences, the influence of disease status and medication history [14].

Prospective studies are better able to exclude the interference of multiple confounders and more scientifically explore the association of sarcopenia with osteoporosis and fracture. A prospective study enrolled 1089 volunteers with a mean age of 62 years, 51% for female, with a total of 563 individuals experiencing a fracture during a mean follow-up of 10.7 years. It was reported that sarcopenia in men have lower spine and total body BMD, higher nonvertebral fracture rates, and sarcopenia in women have lower total hip BMD [15].

A prospective study of 2,941 elderly people aged 70 to 79 years, with 63 hip fractures occurring during the follow-up of 6.6 years, showed that reduced bone mineral density, muscle mass, muscle strength and function, and increased intermuscular fat mass were associated with an increased risk of hip fracture [16]. The prospective study of about 2,000 men over the age of 65 community residents of Hong Kong in China, showed that 226 males (11.3%) had at least one fracture during the follow-up of 11.3 years. The results showed that sarcopenia was an independent risk factor for fractures besides bone mineral density and other fracture risk factors (hazard ratio was 1.87). If combined with sarcopenia and osteoporosis, the risk of fracture was ~~will be~~ further increased (hazard ratio is 3.49) [17]. GERICO cohort study included 913 cases of community residents, with an average age of 65.0 years. The follow-up time was 3.4 + 0.9?? years, 40 cases (4.4%) ~~participants had were~~ at least one fragility fracture. The results show that decreased muscle mass significantly increased fracture risk (odds ratio 2.32). If the sarcopenia combined hip or spine T score was < 2.5, the risk of fragility fracture was ~~will~~ further increased significantly (odds ratio, 3.39) [18]. Therefore, prospective studies have confirmed that sarcopenia and osteoporosis are important risk factors for fragility fracture. Sarcopenia may be considered to have potential predictive value for fracture risk, and joint evaluation of osteoporosis and sarcopenia may help to identify these high-risk fracture patients who need prevention and / or treatment.

A meta-analysis of sarcopenia and falls and fractures in the elderly in 2019 included 17 studies, and showed that patients with sarcopenia had a significantly higher risk of fracture than those without sarcopenia (cross-sectional study: combined OR=1.840; prospective study: combined OR=1.71)[19]. The association between sarcopenia and fracture remains significant. The subgroup analysis showed that skeletal muscle loss was significantly associated with fracture independent of study design, population, gender, region, and study quality.

**Genetic association between osteoporotic fractures and sarcopenia**

Fracture is considered to be the most serious clinical outcome of osteoporosis. Genetic susceptibility, old age, female gender, falls and low bone mineral density are the strongest determinants of fracture risk [20]. A positive family history of hip fractures is an important risk factor for osteoporosis and fractures, thus reinforcing the role of genetics in the pathogenesis of osteoporotic fractures [21]. Studies on twins and families with diseases estimated that the heritability of bone mineral density was as high as 80-90%, while the heritability of lean mass was 70-88%, and the genetic correlation between them was 46% [22]. The heritability of osteoporotic fractures is 50-60% [23]. ~~It~~ This suggests that genetic factors play an important role in osteoporotic fracture and sarcopenia, but the disease-related genetic loci and susceptibility genes found in the present study are far from sufficient to explain the shared genetic susceptibility.

As bone and muscle cells share the same mesenchymal precursor, it is hypothesized that bone strength and muscle mass share genetic determinants in adults. Since there ~~are~~ is clinical evidence that osteoporotic fractures are positively related to sarcopenia, sarcopenia may be a potential predictive value for fracture risk~~, which~~ suggesting that there may be ~~the~~ sharing of genetic determinants between the development of sarcopenia and osteoporotic fracture.

~~Up to now,~~ The meta-analysis of the genetic factors for osteoporosis (GEFOS) and genetic markers for osteoporosis (GENOMOS) consortia(39) (31,016 cases and 102,444 controls) was a breakthrough in which the strongest relevant BMD markers accounted for about 6% of BMD variation. In addition, 14 of 56 BMD loci were associated with fracture at Bonferroni adjusted significance level, and 6 of them were related at genome-wide significance level (P < 5e-8), including 18p11.21 (fam210a), 7q21.3 (SLC25A13), 11q13.2 (LRP5), 4q22.1 (MEPE), 2p16.2 (sptbn1) and 10q21.1 (DKK1). Recent studies have confirmed that FAM210A is a novel determinant of bone and muscle structure and strength [25]. The role of FAM210A gene (in what?) has been demonstrated in knockout mice. Therefore, FAM210A gene plays an important role in regulating bone structure and function, which may affect osteoporosis through biological pathways and other mechanisms involved in muscle physiology??.

An alternative measurement method for DXA is total-body bone mineral density, which is commonly used in childhood and adolescence, where GWAS recently reported that more than 80 loci interpreting 10% of the variance [26]. This publication examined these SNPs in an independent fracture study, where a decrease of one standard deviation in a genetically determined total-body BMD that resulted in 56% higher odds of fracture. Another phenotype is BMD estimated from quantitative heel ultrasound, where 12 out of the associated 307 SNPs were associated with fracture risk, and the AQP1 and SLC8A1 loci newly were added as potential genetic determinants of fracture[27] .

In the past, most of the genes associated with fracture risk have been identified by detecting known BMD gene loci. To date, there are two GWAS with a vertebral fracture as the endpoint. In the first meta-analysis of GWAS, a single locus on chromosome 16q24 (rs11645938) was associated with the risk of radiographic vertebral fracture, which was not repeated in 5720 cases and 21791 controls [28]. Another recent meta-analysis of GWAS reported that chromosome 2q13 locus was significantly associated with clinical vertebral fractures independent of bone mineral density [29]. The first GWAS study of non-vertebral osteoporotic fractures (n=700) was conducted in Chinese elderly and ALDH7A1 was identified as a fracture-related site [30]. However, the gene was not replicated in any large meta-analysis in Europe. In 2018, Trajanoska et al. [31] conducted the GWAS study of the largest osteoporotic fractures, involving 37,857 cases and 227,116 controls, which were replicated in nearly 300,000 people (including 147,200 cases). Overall, this effort identified 15 fracture loci with moderate validity (SPTBN1, CTNNB1,ESR1,RSOP3,SHFM1, MBL2/DKK1, LRP5,SOST, CPED1/WNT16, GRB10/COBL,FUPB3, RPS6KA5, STARD3NL,ETS2 and FAM210A loci). Additionally, RSPO3,ESR1, GRB10/COBL , and ETS2 loci were indentified to the list of novel fracture loci. Interestingly, all identified loci are known BMD loci. In general, these SNPs had less effect on fracture than on bone mineral density. Therefore, genetic effects of all types of fractures are mediated through gene regulation of BMD.

However, the risk of fracture is not entirely determined by the intrinsic nature of bone, as other external factors are known to play a role, for example skeletal muscle loss, fall-related factors. Therefore, it is increasingly recognized that osteoporosis does not account for all low-trauma fractures [32]. Similar to other characteristics and age, the genetic capacity of fracture risk also decreases with age. ~~Learning~~ ?? phenotypes associated with fracture risk, such as bone mineral density, leanmass, and grip strength, may be a good choice to study the genetic basis of fracture risk[33]. *This sentence does not make sense. Please reword.*

Given that bone and muscle cells come from the same mesenchymal precursor, and that muscle and bone are directly linked, it is thus plausible that there are underlying pleitropic genes that determine both traits. A high genetic correlation between femoral geometric parameters and total body lean mass was reported in white American adults from Nebraska, ranging from 0.28 to 0.69[34]. In addition, a recent bivariate genomic linkage analysis found that two chromosomal regions, 5q35 and 10q24, had pleiotropic effect on these phenotypes in the same sample[35]. Our preliminary results in the Framingham Osteoporosis study show a high bivariate genetic correlation between leg lean mass and the cross-sectional geometry of femoral, ranging from 0.56 to 0.81[36].

At present, studies have reported that AR, ESR, IGF-1, myostatin (GDF8 gene), VDR, LRP5 and IL6 are candidate genes for regulating bone and muscle metabolism through various pathways, including inflammation, growth hormone and steroid metabolism. Other possible candidate genes, such as leptin (LEP), transcription factor SRY box 17 (SRY-17), pleiotropic growth factor (PTIN), resistin (RETN), vascular endothelial growth factor (VEGF) and glucocorticoid receptor (GCR) [33 ].

IGF-1 encodes a key enzyme in the steroid hormone pathway producing progesterone, adrenocorticotropic hormone, glucocorticoid, estrogen and androgen. It acts on GH / IGF-1 axis and jointly affects the development and growth of bone and muscle [37] . Vitamin D receptor (VDR) gene has been considered as one of the genetic determinants of bone state, which regulates bone homeostasis through vitamin D endocrine system. Vitamin D supplementation can increase bone mineral density or bone strength, but also reduce the incidence of falls and fractures. This phenomenon may be due to the relationship between VDR polymorphism and muscle strength [38] [39]. Multiple studies have provided evidence that VDR polymorphism is associated with skeletal geometry [40], fracture [38], and muscle mass or strength [41, 42].

LRP5, a Wnt common receptor, has been proved to be related to BMD and is ~~very~~ important for bone metabolism [43]. Genetic variation studies found that the polymorphism of LRP5 gene can regulate the relationship between physical activity and bone mineral density in men, suggesting that LRP5 may play a role in bone adaptation to mechanical load in humans [44]. In addition, the Wnt signaling pathway is related to skeletal muscle hypertrophy induced by overload in mice [45] . In conclusion, these studies may indicate that the Wnt signaling pathway, especially LRP5, may be involved in the interaction between bone and muscle. Myostatin is a member of the TGF ‐ β superfamily and a negative regulator of skeletal muscle mass [36]. Myostatin may act on bone and muscle tissue upstream of Wnt signal [46 ]. IL-6 is an inflammatory cytokine, that plays an important role in bone and muscle loss [47]. IL-6 has been proved to be a high level of IL-6 produced by human skeletal muscle after endurance exercise, which plays a certain role in supporting the mobilization of metabolic matrix in human exercise. The best study associated osteoporosis with IL-6 was a SNP G / C mutation at 174bp, which was shown to be associated with increased risk of wrist fracture [48] and lower hip BMD in postmenopausal women [49] and de fat-free mass in men but not women[50] . In vitro studies have shown that IL-6 inhibits the secretion of IGF1; therefore, the negative effect of IL-6 on muscle function might be mediated by IGF1 [51] .

Bone mineral density and lean mass are hereditary traits. In 2017, Medina Gomez et al estimated the heritability of shared SNP and performed a bivariate GIS meta-analysis of total body lean mass (TB-LM) and total headless bone mineral density (TBLH-BMD) regions in 10,414 children. The SNP heritability of TBLH-BMD is estimated to be 43% (95% CI: 34-52%), and that of TB-LM to be 39% (95% CI: 30-48%),and the common genetic component was 43% (95% CI: 29-56%).Eight polymorphic loci with pleiotropic effect were identified, including seven established BMD loci: WNT4, GALNT3, MEPE, CPED1/WNT16, TNFSF11, RIN3, and PPP6R3/LRP5.In the TOM1L2/SREBF1 locus, the mutant had opposite effects on TB-LM and TB-BMD, and were strongly correlated with TB-LM. In vitro, SREBF1 was found to be expressed in mouse, human osteoblasts and human muscle tissues.This is the first GWAS meta-analysis using BMD and muscle mass as bivariate to demonstrate the pleiotropic genetic loci on BMD and lean mass[52]. Recent GWAS studies suggested that the encoding genes of MYOSTATIN, actin 3(-actinin3), activator receptor co-activator 1- (PGC-1), myocyte enhancer factor 2C(MEF-2C), GLYAT and METTL21C are also closely related to sarcopenia and osteoporosis [53].

In recent years, GWAS studies have found that both lean mass and hand grip strength are associated with fracture risk [54], which may provide a possible endophenotype for elucidating the potential genetic study of fracture risk. It is thought that this relationship may be due to a negative relationship between muscle strength and balance, and the risk of fall. Zillikens et al. [55] found five SNPs located near HSD17B11, VCAN, ADAMTSL3, IRS1 and FTO in 10,1767 individuals, and three SNPS near VCAN, ADAMTSL3 and IRS1 in 73,420 individuals were correlated with appendicular lean mass. Karasik et al.[56] identified a new lean mass locus at TNRC6B.

GWAS of grip strength reported by Willems et al confirmed that there were 16 novel loci associated with grip strength, including genes related to the structure and function of skeletal muscle fiber (ACTG1), neuron maintenance and signal transduction (PEX14,TGFA,SYT1), or monogenic syndromes (PEX14,LRPPRC and KANSL1) related to psychomotor disorders. In addition,the authors found evidence that bone mineral density, lean mass and grip strength share a common genetic etiology in the same study, and suggest that higher grip strength and lower fracture risk have a causal effect [57] . Similar results were found in the study of Trajanoska, which found a potential causal relationship between grip strength and fracture risk, but the multitest significance threshold could not be replicated [31]. However, GWAS has found some SNPs or genes related to fracture risk, as a complex genetic disease, this is only the tip of the iceberg for osteoporotic fracture, which is far from enough to explain the complex genetic mechanism and pathogenesis of osteoporotic fracture *(This sentence needs to be reworded).* In order to get better prevention and treatment of the disease, more advanced methods are still needed to mine more pleiotropic genetic loci. This work will help us to better explore the pathogenesis of osteoporotic fracture.

**Summary**

~~To sum up,~~ ~~Understanding~~ More knowldege of the clinical and genetic correlation between osteoporotic fracture and sarcopenia ~~is~~ would be helpful to understand the interaction between muscle and bone, and provide the rationale to study the etiology of this complex musculoskeletal disease condition, ~~so as to~~ and create a drug / intervention ~~method~~ strategy for the future studies. ~~This therapy can be used~~ These types of studies could have a huge therapeutic impact on the ability to reverse sarcopenia in the elderly, prevent muscle loss in astronauts, and combat falls and fractures. ~~These advances could~~  and translate into new ways to prevent osteoporotic fracture and sarcopenia. Moreover, ~~it may~~ this strategy will ultimately help to understand broader concepts such as fraility. Identification of potentially important genetic variations in bone and muscle~~,~~ measured~~ment~~ with state-of-the-art technology, and replication experiments in preclinical and clinical studies, ~~in large humans and animals~~ will provide valuable potential targets and pharmacogenetic applications for osteoporotic fractures. ~~and~~ ~~pharmacogenetic applications for important research.~~

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