Factors Affecting Peak Bone Mass

Subjects: Rheumatology

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Peak bone mass is the amount of bone tissue that is formed when a stable skeletal state is achieved at a young age. To date, there are no established peak bone mass standards nor clear data on the age at which peak bone mass occurs. At the same time, the level of peak bone mass at a young age is an important predictor of the onset of primary osteoporosis.

peak bone mass PBM aBMD bone mineral density

1. Hormonal Background

One of the key roles in the regulation of bone metabolism is played by sex hormones. Thus, estrogens limit the production of osteoclastogenic cytokines produced by osteoblast cells and thus inhibit osteoclast formation and bone resorption [1]. Changes in the hormonal background in different age periods have a significant effect on bone metabolism. The effect of hormonal background was studied in mice in the most detail. For example, deletion of the androgen receptor (AR) in male mice causes high bone turnover, increased bone resorption, and reduced cortical and cancellous bone mass. Targeted deletion of AR in mature osteoblasts, however, reduces the mass of the bone spongy substance, but does not affect the cortical layer of bone [2]. Over the past 10 years, extensive data have indicated the involvement of oxidative stress in increased bone resorption associated with estrogen or androgen deficiency [3]. RANKL and MCS-F (macrophage colony-stimulating factor) are two cytokines that are necessary for the formation of osteoclasts [4]; they stimulate the intracellular accumulation of H_2O_2, which is necessary for osteoclast adaptation, differentiation, and survival [5]. This hypothesis has been proven empirically: in mice capable of synthesizing human catalase, an enzyme that utilizes H_2O_2 in mitochondria, there was an increase in cortical and spongy bone mass due to a decrease in the number of osteoclasts [2]. In adulthood, certain endocrine pathologies associated with estrogen, such as complete androgen insensitivity syndrome due to complete androgen resistance, premature ovarian failure, or Turner syndrome, can lead to a decrease in aBMD in women at the level of the lumbar spine and femoral neck [6].

On the other hand, it is interesting that gender-supportive hormone therapy in trans women (with estradiol and antiandrogens) and in trans men (with testosterone) resulted in an increase in bone metabolism in young trans men, while it decreased in trans women, demonstrating the crucial role of estrogen in the regulation of bone resorption [7].

2. Microbiome

Intestinal microbiota makes a certain contribution to the metabolism of connective tissue and bone tissue. Yan et al. (2017) reported that short-chain fatty acids (SCFAs) produced by the microbiota induced insulin-like growth factor 1 (IGF-1), which promotes bone growth [8]. Treatment of mice with microbiota metabolism products, including SCFAs, propionate, and butyrate, significantly increases bone mass and prevents postmenopausal and inflammation-induced bone loss, and propionate and butyrate induce metabolic reprogramming of osteoclasts, which leads to suppression of bone resorption activity by osteoclasts [9][10][11]. The consumption of indigestible food components is one of the ways in which it is possible to change the gut microbiota to improve the health of the host. Dietary components, such as prebiotic dietary fiber, are associated with positive shifts in the composition of the intestinal microbial community [12]. A study conducted among adolescents showed that the consumption of various prebiotics, such as galactooligosaccharides and soluble corn fiber, which can be fermented to SCFAs, led to increased absorption of calcium in the intestine and was associated with the relative content of *Parabacteroides*, *Bifidobacterium*, *Bacteroides*, *Butyricicoccus*, *Oscillibacter*, and *Dialister* species measured in feces, and the change in the intestinal microbiome towards enrichment with bacteria of the genera *Dialister* and *Faecalibacterium*, on the contrary, was associated with the presence of osteoporosis [13]. In addition, in clinical trials, it was reported that the consumption of SCFAs in women could improve bone metabolism with increased activity of bone-specific alkaline phosphatase [14]. Supplements with *Bacillus subtilis*, Lactobacilli, and multi-species probiotics have demonstrated a beneficial effect not only on the human gut microbiota [15], but also on markers of bone metabolism [16]. Strain-specific probiotics can reduce oxidative stress by producing several antioxidant molecules, e.g., glutathione, folic acid, and exopolysaccharide. In addition, short-chain fatty acids produced by some gut microbiota may also help reduce oxidative stress by promoting the production of antioxidant molecules [17].

3. Quality Body Composition

The understanding of the effect of adipose tissue on bone metabolism is still ambiguous, and often the results of studies contradict each other. It is worth considering the adipose tissue of the bone marrow and adipose tissue in general. Mesenchymal stromal cells (MSCs) are multipotent progenitors capable of differentiation into osteoblasts and can potentially serve as a source of cell therapy for bone regeneration. Many factors have been shown to regulate the differentiation of MSCs into the osteogenic lineage, such as the cyclooxygenase-2 (COX2)/prostaglandin E_2 (PGE_2) signaling pathway, which is critical for bone repair. PGE_2 binds four different EP1-4 receptors (prostaglandin receptors) [18]. Thus, adipocytes themselves stimulate the differentiation of MSCs into adipocytes, and not into osteoblasts. In addition, adipocytes in the bone marrow microenvironment release a range of pro-inflammatory and immunomodulatory molecules that enhance osteoclast formation and activation, thereby contributing to bone fragility. In vivo analysis of the relative content of saturated and unsaturated fatty acids in the bone marrow indicates a locally dependent marrow fat composition and an association between an elevated unsaturation index and bone health. Most diseases with bone loss, in which an altered composition of the bone marrow develops, have aging and/or chronic inflammation as common factors. Both saturated and unsaturated fatty acids form lipid forms that are active mediators of the inflammatory process [19]. However, the intervention of alpha-lipoic acid (ALA) inhibited the RANKL-induced proliferation and differentiation of osteoclasts. ALA also inhibited bone resorption activity, suppressed RANKL-induced transcription factors c-Fos, c-Jun, and NFATC1

(nuclear factor of activated T cells) in combination with markers of osteoclasts such as TRAP (prediction of affinity for transcription factor), OSCAR (receptor associated with osteoclasts), cathepsin K, and β3-integrin [20]. On the other hand, excessive accumulation of adipose tissue performs the role of a mechanical vertical load contributing to the build-up of bone tissue. In this case, bone quality and structure are the result of a balance of inflammatory and mechanical incentive stimuli [21].

Data on the influence of sex on body mass index (BMI) and aBMD are also contradictory. There is a point of view that aBMD values increase with an increase in BMI only in men [22]. Nevertheless, a number of authors have noted that increasing BMI to the values of the “metabolic syndrome” leads to decreasing aBMD for both men and women [23]. In another study among young Hispanic and non-Hispanic girls, Megan Hetherington-Rauth et al. found a positive contribution of fat mass to bone strength in vBMD; however, negative associations were also found with the content and thickness of the cortical bone of the radius [24]. Also, Zeyu Xiao et al. in a sample of young Chinese adults found that both total lean body mass and fat mass were significantly positively associated with aBMD in both genders [25]. Nielsen et al. obtained results that individuals aged 15–19 years who lost weight during follow-up showed slower progression of aBMD gain compared to those who gained weight, but weight loss or BMI reduction over 2 years was not associated with a net loss of aBMD [26].

In a study on FAT-ATTAC transgenic mice, Lagerquist et al. induced adipocyte apoptosis and assessed bone metabolism by X-ray absorptiometry and found no effect of adipose tissue reduction on bone resorption [27].

Bones and muscles are two deeply interconnected organs with integrated growth and locomotion [28]. In a study involving 416 women and 334 men aged 20 to 30 years in Vietnam, the association of body composition and aBMD at the lumbar spine and femoral neck was assessed using dual-energy X-ray absorptiometry. Peak aBMD in men was higher than in women, and the difference was more pronounced in the femoral neck region than in the lumbar spine, and fat-free mass was the only predictor of aBMD for both men and women. Each kilogram of increase in muscle mass was associated with an increase in BMD by about 0.01 g/cm^2 [29]. Winther et al. also found that higher levels of aBMD corresponded to higher levels of fat-free mass in both genders, but higher aBMD at higher levels of fat mass was found only in girls [30].

Muscle paralysis also contributes to bone mineral density. Paralysis caused by botulinum toxin causes bone loss in adult mice and slows down the healing of fractures [31].

Bones and muscles act as secretory endocrine organs that affect each other’s function. Biochemical crosstalk occurs through myokines such as myostatin, irisin, interleukin IL-6, IL-7, IL-15, insulin-like growth factor-1, fibroblast growth factor, and β-aminoisobutyric acid, as well as through factors of bone origin, including FGF23, prostaglandin E_2, transforming factor growth of β, osteocalcin, and sclerostin [32]. Myostatin is member of the transforming growth factors-beta (TGF-beta) superfamily, which is highly expressed in skeletal muscles. Loss of myostatin function in mice led to an increase in muscle mass, increased bone formation, and an increase in bone cross-section in most anatomical areas, including limbs, spine, and jaw in mice [33]. Myostatin inhibitors such as ACVR2B/Fc, a soluble myostatin decoy receptor, have been shown to prevent loss of both muscle and bone tissue

in models of muscular dystrophy [34]. In vitro studies on mice have also shown that myostatin enhances RANKL-induced osteoclastogenesis [35]. Myostatin is also expressed in the early stages of fracture healing, and myostatin deficiency leads to an increase in the size and strength of the callus during fracture. Taken together, these data suggest that myostatin may affect the proliferation and differentiation of osteogenesis progenitor cells and that myostatin antagonists and inhibitors may be therapeutically useful for increasing both muscle mass and bone. Myostatin directly affects osteocyte function by suppressing exosomal *miR-218* microRNA and thus inhibits osteoblast differentiation [36].

4. Smoking

The negative impact of smoking on various systems and organs is multifaceted. Mattias Callréus et al. investigated the effects of smoking among women aged 25 years, but statistically significant differences were found only in the levels of aBMD of the femoral neck. Similarly, lower aBMD, in comparison with the control, persisted for up to 24 months after quitting smoking, becoming comparable to those who had never smoked after 24 months [37]. To further evaluate these outcomes, a meta-analysis of 14 prospective studies, information was conducted, which showed that, compared with those who have never smoked, cigarette smoking increased the risk of hip fracture in men, especially in current smokers [38]. Another study has also found an association between smoking and an increased risk of fractures [39]. Both active and passive smoking negatively affect bone mass; quitting smoking seems to reverse the effect of smoking and improve bone health [40]. In men, regardless of age, method, and site of bone density measurement, cross-sectional studies showed that smokers had significantly lower aBMD than non-smokers [41]. In bone studies, smoking was associated with lower aBMD, increased risk of fractures, periodontitis, loss of alveolar bone, and rejection of dental implants [42]. In a large NHANES III study involving 14,500 subjects, the bone mineral density of the femoral neck in smokers was numerically lower than in never-smokers, but the statistical significance of the difference was not reached [43][44]. The data on cannabis smoking are contradictory. Thus, bone mineral density (Z-criterion) was significantly lower in avid cannabis users compared to the control group in the lumbar spine, hip neck, and hip as a whole [45]; however, it was found that the cannabinoid receptors CB1 and CB2 were expressed in bones and regulate bone homeostasis in rodents and humans. Cannabis treatment has been shown to improve fracture healing in rats [46].

5. Nutritional Deficiencies (Calcium, Vitamin D, Phosphorus), Lipids, and Food Character

The contribution of calcium and vitamin D to the quality of bone tissue is beyond doubt; the use of sufficient amounts of calcium and vitamin D in childhood and adolescence is of the greatest importance. Vitamin D synthesized in the skin or absorbed with food undergoes a multi-step enzymatic transformation into its active form, 1,25-dihydroxyvitamin D, [1,25(OH) 2 D], followed by interaction with the vitamin D receptor (VDR) to modulate the expression of the target gene [47]. Vitamin D can support skeletal health and improve bone mineralization by increasing calcium absorption in the intestine, reducing secondary hyperparathyroidism, and reducing bone resorption [48]; moreover, increased calcium intake in combination with vitamin D reduces the rate of loss of

minerals in the bones without harm to the intestinal microbiota. Guo-Hau Gou et al. described the positive effect of daily intake of vitamin D and magnesium on hip neck aBMD in female participants aged 8–11 years [49]. Zhou also proved that higher intake of calcium and vitamin D was associated with higher total hip and hip neck aBMD in young men (16–18 years old), and cumulatively high levels of calcium and vitamin D intake over time contributed to better maintenance of aBMD in the lumbar spine and femurs in adult women [50]. Neville et al. also described the positive effect of vitamin D on hip neck aBMD in adolescent girls, but not in the lumbar spine [51]. Krstic et al. described the positive effect of vitamin D intake and physical activity on young mice, explaining the mechanism by hypomethylation of the RXRA (Retinoid X Receptor Alpha) gene DNA, which together with the vitamin D receptor forms a mechanism that transmits the nuclear effects of vitamin D [52].

The question of the effect of dietary lipids on bone tissue remains open. In a mouse study, a high-lipid diet (HLD) resulted in osteoclast activation, a decrease in trabecular bone volume, along with an increase in bone marrow deposition compared to a low-fat diet group [53]. In addition, HLD led to an increase in bone marrow adipose tissue and changes in the bone marrow microenvironment along with a pro-inflammatory environment, which could contribute to a negative effect on bone metabolism. At present, the effect of adipose tissue on bone metabolism is not fully understood [54].

6. Physical Activity, Lifestyle, Psychoemotional Status

There is a positive relationship between the incidence of fractures and the level of physical activity due to the increased risk of falls during physical activity. Thus, although physical activity is critical for bone modeling, children with higher levels of physical activity are more likely to have fractures [55]. Weekly physical activity has a positive effect on BMC and bone mineral density in both boys and girls during puberty when exercising 1–2 times a week [56]. Physical exercises at school in terms of time are effective for increasing aBMD and/or vBMD in children and adolescents, but should include high-intensity exercises, such as high-impact jumps [57]. Physical activity 3 times a week for 40 min in ball games or circular strength training throughout the school year improves bone mineralization and some aspects of muscle fitness of children aged 8–10 years, suggesting that well-organized intensive physical education classes can positively affect the development of the musculoskeletal system and health in children early age [58].

Sleep also affects bone mineralization. An unbalanced sleep pattern contributes to bone loss and an increased risk of osteoporosis. Thus, healthy sleep contributes to the prevention of osteoporosis [59].

Psychoemotional status, as well as associated pathological conditions, also affect bone health. So, depression was associated with lower aBMD, especially in the spine, in white men, and non-highly educated populations. Moreover, people with depression were more likely to suffer fractures and osteoporosis [60].

7. Early Antropometric Characteristics

Body length at birth and height under the age of 7 years were positively associated with mineral density of the femoral neck, and growth in all studied age periods was positively associated with the area of the spine. Growth under the age of 7 years was associated with the mineral density of the femoral neck [61]. Bone mineral density may also be affected by birth weight, among other things. In a meta-analysis by Baird et al. (14 studies involving men and women aged 18–80 years), a positive relationship was found between birth weight and aBMD of the lumbar spine in adulthood, and this relationship was stronger for women [62]. This hypothesis was also confirmed in the PEAK-25 study conducted in Sweden (1061 women aged 25 years) [63].

8. Heredity and Genetics

Data regarding the association of PBM with genes and polymorphic variants in humans are incomplete [64][65]. Wei-jia Yu and colleagues (2020) reported associations between polymorphic variants of the gene *LGR4* (Leucine Rich Repeat Containing G Protein-Coupled Receptor 4) and bone metabolism. Their study involved 1296 participants from nuclear families (mother, father, son) and they found an association of polymorphic variants *rs11029986* and total hip aBMD and *rs12796247*, *rs2219783* with lumbar spine aBMD [66]. Another study by Zheng et al. (2016) described associations of six SNPs (*rs6126098, rs6091103*, *rs238303*, *rs6067647*, *rs8126174*, and *rs4811144)* in the *CTNNBL1* gene (Beta-catenin-like protein 1) and peak bone mineral density of the lumbar spine, femoral neck, or the entire femur [67]. Zhao et al. (2017) conducted a study on 1296 Chinese men and found positive associations between *rs9585961 METTL21C* (Methyltransferase Like Protein 21C) and aBMD of the lumbar spine and femoral neck, as well as *rs9518810* and aBMD of the femoral neck [68]. In a separate study, He et al. (2011) analyzed 401 Chinese nuclear families and described an intrafamily negative relationship between allele C *rs16878759* and PBM of the lumbar spine. They also found that the CCC haplotype (containing *rs12699800*, *rs16878759*, and *rs17619769*) had a significant intrafamily association with PBM of the lumbar spine [69]. Chesi et al. (2019) conducted a study using a donor culture of primary MSC. *ING3* (Inhibitor of Growth Family Member 3) and *EPDR1* (Ependymin Related 1) knockdowns disrupted osteoblast differentiation and increased MSC adipogenic differentiation. *ING3* knockdown increased adipogenesis by 8 times, and *EPDR1* knockdown by 3.5 times [70]. Furthermore, this group of authors, in a repeated experiment with editing the *EPDR1* gene by CRISPR-Cas 9 on an immortalized MSC hFOB1.19 cell culture, confirmed the important role of *EPDR1* in osteoblast differentiation [71].

The search for genes involved in bone metabolism continues in mouse models. In modified mice with Wnt16$^{-/-}$ knockout, the thickness of the cortical layer of bone and bone strength were reduced [72]. An intronic variant *rs2566752* was associated with aBMD of the spine. A less common allele C from this locus was associated with increased spinal aBMD. This allele was also found to be associated with a reduced risk of fracture in the TwinsUK cohort [73]. Fibroblast growth factor receptor 1 (*FGFR1*) is an important molecule for skeletal development and bone remodeling. Mice lacking *FGFR1* in osteocytes showed an increase in trabecular bone mass at 2 and 6 months of age as a result of increased bone formation and reduced resorption [74].

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