INVITED REVIEW

TRENDS in
Sport Sciences
2016; **2**(23): 63-71
ISSN 2299-9590

The role of physical activity in bone metabolism and osteoporosis prevention

MONIKA DALZ, EWA ŚLIWICKA, ANNA HUTA-OSIECKA, ALICJA NOWAK

Abstract
Introduction. The attainment of peak bone mass in childhood and early adolescence can be ensured by proper diet, which includes a high intake of calcium and vitamin D, and by an adequate level of physical activity. During the period of skeletal involution physical exercise can reduce the rate of bone resorption, and improve motor coordination and prevention of falls. Aim of Study. The aim of the review is to discuss present-day views regarding the effects of physical activity on bone metabolism, and in particular, on osteoporosis prevention. Authors studying the effects of physical activity on bone tissue often classify physical exercises according to the volume of mechanical loads related to gravity and muscle strength. The reaction of bone tissue to mechanical loading depends on the frequency and intensity of the loads. Different forms of physical activity can be classified into *weight-bearing*, in which the athlete's skeleton is loaded by the athlete's own body weight, and *non-weight-bearing*. The forces acting on bone tissue in result of muscle contractions may additionally affect bone metabolism in loaded sites, and the resulting bone deformations inhibit resorption during bone remodeling. At later stages of life, prevention of falls becomes highly significant, that is why physical exercise should be aimed at the development of mass and muscle strength. In recent years there has been a growing interest in the role of vitamin D in proper bone mineralization and regulation of muscle strength and functional state of muscles. The intake of sufficient levels of vitamin D significantly lowers the risk of falls. Conclusion. Physical activity is a very important determinant of proper bone metabolism, both in pubescence and during skeletal involution. Physical activity is also conducive to the maintenance of muscle mass, which is an important element of osteoporosis prevention. Due to the crucial role of vitamin D in maintaining the proper condition of the musculoskeletal system various forms of outdoor physical activity are highly recommended.

KEYWORDS: bone, physical activity, vitamin D.

Received: 13 May 2016
Accepted: 25 June 2016

Corresponding author: anowak@awf.poznan.pl

Poznan University of Physical Education, Department of Hygiene, Poznań, Poland

What is already known on this topic?
Physical activity is a very important factor in maintenance of proper bone metabolism and muscle mass, in pubescence as well as during skeletal involution. That can potentially increase or maintain bone mass and strength, and reduce the risk of falls in older populations, which is associated with the prevention of sarcopenia.

Osteoporosis, which is characterized by low bone mass and distortions of bone microarchitecture entailing an increased risk of fractures, is a serious social problem. The growing prevalence of osteoporosis is associated with the rising population of elderly people and lifestyle changes. In 2010, about 22 million women and 5.6 million men suffered from osteoporosis in the European Union. In the same year, there were 3.5 million reported bone fractures, including the hip fractures (610,000 cases), vertebral fractures (520,000 cases), the forearm fractures (560,000 cases), and other parts of the skeleton, e.g. the pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum, and femur [1].

There are two general strategies of making the skeleton more resistant to fracture: 1) maximizing the gain in BMD in the first three decades of life; and 2) minimizing the decline in BMD after the age of 40 due to endocrine changes, aging, or other factors such as decline in physical activity [2].

The attainment of peak bone mass in childhood and early adolescence can be ensured by proper diet, which includes a high intake of calcium and vitamin D, and by a high level of physical activity [3, 4]. Michalopoulou et al. [5] showed that a high level of physical activity before puberty has a greater effect on long bone geometry, the size of cortical bone, and that the density of cortical and cancellous bone in girls with high levels of physical activity is higher than in their more physically passive counterparts. Bielemann et al. [6] noted a significant correlation between participation in sport activity of young people aged 11-15 years and the BMD of the femoral neck and lumbar spine measured after 18 years of age.

During the period of skeletal involution an inactive lifestyle leads to a faster decrease in bone mass, while increased physical activity can inhibit this decline [2, 7]. Feskanich et al. [8] in their study of postmenopausal women noted a reduced risk of hip bone fracture along with increasing physical activity. Furthermore, the undertaking of regular physical exercise by the elderly improves muscle strength and motor coordination, which reduces the risk of falls and fall-related bone fractures [2, 9, 10, 11]. Sarcopenia, i.e. the degenerative loss of skeletal muscle mass associated with aging, impairs muscle strength, general fitness and quality of life [12].

The significant impact of physical activity on bone metabolism has been confirmed by numerous studies on animals and humans [2, 13, 14, 15, 16]. Many authors show that after years of training athletes do have higher bone mineral density than non-training individuals at a similar age [17, 18, 19, 20, 21]. Significantly higher BMD in different parts of the skeleton was found in athletes representing such sports as gymnastics [22, 23], modern dance [24], jogging [25], tennis [26, 27], judo [20, 28], water polo [28], wrestling [20], basketball [29], volleyball [30], rugby [31, 32], handball [33], and soccer [34].

Numerous studies point to bone mass losses when bone tissue is deprived of the impact of the gravity force, e.g. during long-term immobilization. This is associated with the lack of mechanical loading of bones as well as losses in muscle mass [35]. According to some authors, the mechanical loads of bones result from the impact of gravity and ground-reaction forces as well as muscle-reaction forces [19].

Osteocytes are regarded as the primary sensors of mechanical loads in bone tissue [36, 37]. Under the mechanical impact bone tissue is subject to stress and compressive forces causing tissue deformations, which induces an increased flow of the intraosseous fluid and generates streaming electric potentials [37, 38]. The latter stimulate osteocytes, regardless of the stimulation by the osseous fluid flux, which exerts a pressure on bone cell membranes [39]. Both factors contribute to the processing of mechanical stimulus into cellular response which leads to changes in the bone tissue structure [40]. The effect of mechanotransduction is the mechanism of bone tissue remodeling [41].

The skeleton is sensitive to mechanical stimulation at each stage of life; however, the bone tissue is more adaptable to structural changes before attaining the peak bone mass. The positive effects of physical activity are also observable at later stages of life, during which physical exercise usually leads to a decreased bone resorption rate, and improves motor coordination and fall prevention [42, 43]. The response of bone tissue to mechanical loading also depends on sex, genetic determinants, comorbidities, available nutrients, used drugs, or other biochemical factors [44].

The response of bone to mechanical loading depends on the type of mechanical stimuli. An important determinant of bone remodeling is the load size [45]. According to Harold Frost's Mechanostat theory in order to induce bone growth reaction the strength of the stimulus should exceed the threshold of tissue sensitivity to mechanical loads [46]. Skerry [47] points out that the stimulated bone mass growth is the result of tissue adaptation to increased mechanical loads. Rubin and Lanyon [45] found in their study on an animal model that this mechanism is not only determined by the volume of mechanical loads but also by the type of tissue tensions, in particular, the impact of compressive forces. Moreover, dynamic loads were shown to be of greater significance to the stimulation of bone remodeling than static loads [48]. An important role is also played by the load frequency [49, 50]. The sensitivity of bone to mechanical loads decreases during steady loading, and this is why interval stimulation is more effective than continuous stimulation [51].

The significance of mechanical loads for bone growth has been confirmed by studies on athletes representing different sports. BMD is greatly affected by physical activity that significantly loads the skeleton [19, 52, 53]. Examples of such activity include resistance training [54, 55, 56, 57] and exercises involving great movement dynamics [20, 58]. In the comparison of BMD of the lumbar spine and the femoral neck in athletes of different sports Platen et al. [20] observed the greatest bone growth effects in athletes of sports involving quick, intense, and diverse body movements (jumps, short accelerations, quick stoppages). Exercises of lower loads, e.g. cycling, swimming, shooting, horse riding, water polo, bowling and billiards were shown to have a less significant impact on BMD changes [22, 59, 60, 61].

The effects of mechanical loads on bone tissue are confirmed by authors who observed that the bone mass of the dominant limb was significantly greater than the bone mass of the non-dominant limb in athletes after many years of training or on completion of their sports career. This was in particular noted in squash [62], tennis [63], volleyball [64] and basketball players [29]. Moreover, Kannus et al. [65] in a study of tennis and squash players noted that the difference in bone mass between the dominant and non-dominant arms was two-times to four-times bigger in athletes who began their sports career before or during puberty than in athletes who took up training about 15 years later. The aforementioned research confirms that bone sensitivity to mechanical loads depends on the stage of life. Thus such factors as the age of training commencement and sporting experience are crucial for bone mass growth [34, 66, 67].

As far as the significance of body weight for bone cell response is concerned some authors distinguish between weight-bearing sports in which the athlete's skeleton is loaded with the athlete's own body weight, e.g. volleyball, basketball, dance, soccer, rugby and squash; and non-weight-bearing sports in which the athlete's skeleton is offloaded or supported, e.g. cycling or rowing [19, 68].

Impact exercise, i.e. exercise consisting of overcoming one's own body weight, is to a large extent associated with the effects of ground forces on bone tissue. In the resistance exercises or exercises during which the athlete's body is supported, the main bone growth stimuli are contracting muscles [69, 70]. Yung et al. [70] observed that the most beneficial for bone tissue are weight-bearing exercises and exercises involving significant impact of the ground forces.

Despite the confirmed significance of physical activity for proper bone metabolism, some authors reveal a negative impact of training, especially with large training loads, on bone mineral density in some parts of the skeleton [71, 72, 73]. Such studies concerned long-distance runners who displayed lower bone mineral content and BMD in the lumbar spine than non-training controls [74, 75]. Excessive training volume and intensity in endurance sports may disturb hormonal balance, e.g. the level of sex hormones, and thus impair bone metabolism [76, 77, 78]. Moreover, it is assumed that the imbalance between the presence of microdamages in bone due to frequent loading and the rate of bone remodeling is the cause of frequent fractures in athletes [79]. A study on an animal model showed that training with big loads, even exceeding 100% of athlete's body weight, can be less advantageous to bone metabolism than training with smaller loads (8% of athlete's body weight) [80]. Lower BMD was also noted after exercises in a body mass reduction program [81, 82]. Physically active girls and women also feature low BMD, which is one of components of female athlete triad. The Triad is a medical condition involving any one of the three components: 1) low energy availability (EA) with or without disordered eating (DE); 2) menstrual dysfunction; and 3) low bone mineral density (BMD) [83]. Depleted energy resources contribute significantly to the disorders of the menstrual cycle. Low estrogen levels can have a negative impact on musculoskeletal health [84]. Female athletes with irregular menstruation and/or low BMD display bone stress injuries, including a spectrum of stress reactions and stress fractures [85, 86].

In prevention of osteoporosis physical activity is an intervention that can potentially 1) increase or maintain bone mass and strength, and 2) reduce the risk of falls in older populations, which is associated with the prevention of sarcopenia [87].

In recent years the contribution of vitamin D to the regulation of muscle strength and function has been noted [88]. The main source of vitamin D in the human body (about 80%) is its dermal synthesis from 7-dehydrocholesterol (provitamin D) with UVB radiation at wavelengths between 290 and 315 nm. In Poland the optimal insolation for endogenous production of vitamin D occurs only from June to September. Dietary sources meet the human body's demand of vitamin D only to some extent (about 20%). In the human body previtamin D follows a long metabolic pathway. First, cholecalciferol is transported in the bloodstream to the liver, where in the process of hydroxylation it is converted into 25-hydroxycholecalciferol (calcidiol) [89, 90], which is the main vitamin D metabolite in the bloodstream. Calcidiol is also the most commonly used marker of vitamin D status in the human body, because it has a relatively long half-life of 2–3 weeks [91]. It is then converted in the mitochondria of the proximal convoluted tubules of the nephrons into 1,25-dihydroxycholecalciferol (calcitriol) – the hormonal active metabolite of vitamin D, whose concentration is 1000 times higher than calcidiol, however, with the half-life of only 4-6 hours [89, 90]. Hydroxylation in the proximal tubules is the only source of the active metabolite of vitamin D. The activity of mitochondrial 1 α-hydroxylase was observed in other human cells such as macrophages, keratinocytes, the placenta, parathyroid glands, malignant cells, and smooth muscle tissue of blood vessels. It has not been detected in the heart, liver, or adrenal cortex. Outside the kidneys, locally synthesized 1,25-dihydroxycholecalciferol regulates (in an auto and paracrine fashion) important physiological functions of the aforementioned tissues [92].

Biologically active calcitriol, as well as its analogs, affect the target cells through the vitamin D receptor. VDR (55-56kDa) is a ligand activator regulating gene transcription together with other receptors such as glucocoricoids, retinoids, thyroxine, sex steroids, fatty acids and eicosanoids, and is classified as a receptor of stereoid hormones [93]. VDR can be found in more than 30 tissues and organs of the human body: bone, kidneys, intestines, heart, blood vessels, brain, adrenal glands, pituitary gland, smooth muscle and striated muscle [94].

The discovery of VDR in skeletal muscle led to the recognition of its role as a regulator of muscle metabolism [95, 96]. There are three proposed mechanisms by which vitamin D affects muscle strength. The first comprises the direct role of 1,25(OH)2D in protein biosynthesis. By binding to nuclear VDR calcitriol regulates the process of transcription [97, 98]. The second is the modification of calcium transportation in the sarcoplasmic reticulum by increasing the effectiveness and/or the number of binding sites of calcium during muscle contraction [97]. The third mechanism is the contribution of vitamin D to aerobic energy processes as confirmed by a significant relationship between vitamin D and mitochondrial function [99]. Garcia et al. [100] indicated that calcitriol can also increase the amount of VDR in muscle cells and reduce myostatin expression.

Vitamin D deficiency is quite common and related to the geographical latitude (in moderate climate zones the sun exposure (UVB radiation) is not enough to produce sufficient amounts of dermal vitamin D), season of the year, skin pigmentation, air pollution and elevation [101, 102]. Furthermore, the high risk of vitamin D deficiency is observed in individuals suffering from malabsorption, nephritic syndrome, liver diseases, and those who take some medicines increasing vitamin D metabolism, e.g. glucocorticosteroids, anticonvulsants, or immunosuppressants [103, 104].

The level of vitamin D in the human body is marked by the blood level of calcitriol. A 25OHD level below 75 nmol/l (30 ng/ml) is considered a state of insufficiency. Vitamin D deficiency is defined as a 25OHD level below 75 nmol/l (30 ng/ml), and its level below 50 nmol/l (20 ng/ml) is considered severe deficiency [94].

Many authors show that a low 25(OH)D blood level increases the risk of falls in the elderly, while proper vitamin D supplementation (700-1000 IU/day) lowers the risk for up to 19% [105, 106]. Calcitriol regulates the expression of vitamin D receptors in muscle cells and can also promote the diversity of these cells by intensifying the expression of IGF-II follistatin and reducing the myostatin expression [100, 107]. The number of VDR receptors decreases with age, which probably reduces muscle strength in the elderly. In conditions of vitamin D deficiency the muscle function and muscle performence can deteriorate before the appearance of any clinical and biochemical symptoms of bone disease [108]. The calcitriol level as shown by different studies is correlated with muscle contraction force and morphological characteristics of skeletal muscle [109, 110]. Grimaldi et al. [109] in their research on a large population of men and women, found a significant correlation between cacitriol and the isometric and isokinetic force of the upper and lower limbs. In another study on a population of elderly women with the 25(OH)D levels lower than 39 nmol/L in the gluteus medius muscle, the diameter of type II muscle fibers was smaller than in individuals with the correct levels of the metabolite [110]. Snijderr et al. [111] in their study on an elderly population observed that the higher 25(OH)D concentration and lower PTH concentration increase the risk of sarcopenia.

Literature data show that physical exercise increases the demand for vitamin D, and the problem of vitamin D deficiency is also visible in athletes. Hamilton et al. [112] indicated that 91% of Middle Eastern male athletes had an insufficient level of 25(OH)D (<20 ng/ml). In their study population they found no associations between calcitriol levels and sun exposure, wearing clothes, or skin pigmentation. Lovell [113] noted a vitamin D deficiency (below 20 ng/ml) in 33% of studied Australian female gymnasts. Constantini et al. [114] showed that 73% of athletes had an insufficient level of vitamin D: in 80% of indoor athletes and in 48% of outdoor athletes. The most serious vitamin D deficiency was found among dancers (94%), basketball players (94%) and taekwondo practitioners (67%). Hamilton [115], in a study of athletes representing various sports, observed an exceptionally high deficiency of vitamin D in athletes under heavy training loads. Similar conclusions were drawn by Willis et al. [116], who recommended monitoring of vitamin D levels for physically active individuals, since regular exercise does lead to vitamin D deficiency in the human body. On the other hand, Close et al. [117] concluded that vitamin D supplementation ensures the optimal functioning of muscles of athletes in winter time.

In conclusion, physical activity is a very important determinant of proper bone metabolism, both in pubescence and during skeletal involution. Physical activity is also conducive to the maintenance of muscle mass , which is an important factor of fractures prevention. Due to the crucial role of vitamin D in maintaining the proper condition of the musculoskeletal system various forms of outdoor physical activity are highly recommended.

What this study adds?

Vitamin D is necessary for the maintenance of structural integrity and function of the musculoskeletal system, therefore, various forms of outdoor physical activity are highly recommended to improve bone health.

References

1. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013; 8(1-2): 1-115.
2. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling V. Physical activity and bone health. Med Sci Sports Exerc. 2004; 36(11): 1985-1996.
3. Bonjour JP, Chevalley T, Ferrari S, Rizzoli R. The importance and relevance of peak bone mass in the prevalence of osteoporosis. Salud Publica Mex. 2009; 51(1): S5-S17.
4. Borer KT. Physical activity in the prevention and amelioration of osteoporosis in women. Interaction of mechanical, hormonal of dietary factors. Sports Med. 2005; 35(9): 779-830.
5. Michalopoulou M, Kambas A, Leontsini D, Chatzinikolaou A, Draganidis D, Avloniti A, Tsoukas D, Michopoulou E, Lyritis GP, Papaioannou N, Tournis S, Fatouros IG. Physical activity is associated with bone geometry of premenarcheal girls in a dose-dependent manner. Metabol. 2013; 62(12): 1811-1818.
6. Bielemann RM, Domingues MR, Horta BL, Menezes AM, Gonçalves H, Assunção MC, Hallal PC. Physical activity throughout adolescence and bone mineral density in early adulthood: the 1993 Pelotas (Brazil) Birth Cohort Study. Osteoporos Int. 2014; 25(8): 2007-2015.
7. Muir JM, Ye Ch, Bhandari M, Adachi JD, Thabane L. The effect of regular physical activity on bone mineral density in post-menopausal women aged 75 and over: a retrospective analysis from the Canadian multicentre osteoporosis study. BMC Musculoskeletal Disorders. 2013; 14: 253-262.
8. Feskanich D, Willett W, Colditz G. Walking and leisure-time activity and risk of hip fracture in postmenopausal women. JAMA 2002; 288(18): 2300-2306.
9. Eng JJ, Pang MY, Ashe MC. Balance, falls, and bone health: role of exercise in reducing fracture risk after stroke. J Rehabil Res Dev. 2008; 45(2): 297-313.
10. Holviala J, Kraemer WJ, Sillanpää E, Karppinen H, Avela J, Kauhanen A, Häkkinen A, Häkkinen K. Effects of strength, endurance and combined training on muscle strength, walking speed and dynamic balance in aging men. Eur J Appl Physiol. 2012; 112(4): 1335-1347.
11. Peterson MD, Rhea MR, Sen A, Gordon PM. Resistance exercise for muscular strength in older adults: a meta-analysis. Ageing Res Rev. 2010; 9(3): 226-237.
12. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, Sieber C, Stout JR, Studenski SA, Vellas B, Woo J, Zamboni M, Cederholm T. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing. 2014; 43(6): 748-759.
13. Holy X, Zérath E. Bone mass increases in less than 4 wk of voluntary exercising in growing rats. Med Sci Sports Exerc. 2000; 32(9): 1562-1569.
14. Iwamoto J, Takeda T, Sato Y. Effect of treadmill exercise on bone mass in female rats. Exp Anim. 2005; 54(1): 1-6.
15. Morel J, Combe B, Francisco J, Bernard J. Bone mineral density of 704 amateur sportsmen involved in different physical activities. Osteoporos Int. 2001; 12(2): 152-157.
16. Singh R, Umemura Y, Honda A, Nagasawa S. Maintenance of bone mass and mechanical properties after short-term cessation of high impact exercise in rats. Int J Sports Med. 2002; 23(2): 77-81.
17. Andreoli A, Celi M, Volpe SL, Sorge R, Tarantino U. Long-term effect of exercise on bone mineral density and body composition in post-menopausal ex-elite athletes: a retrospective study. Eur J Clin Nutr. 2012; 66(1): 69-74.

18. Drenjančević I, Davidović Cvetko E. Influence of physical activity to bone metabolism. Med Glas. 2013; 10(1): 12-19.
19. Morseth B, Emaus N, Jørgensen L. Physical activity and bone: the importance of the various mechanical stimuli for bone mineral density. Norsk Epidemiol. 2011; 20(2): 173-178.
20. Platen P, Chae E, Antz R, Lehmann R, Kühlmorgen J, Allolio B. Bone mineral density in top level male athletes of different sports. Eur J Sport Sci. 2001; 1(5): 1-15.
21. Tveit M, Rosengren BE, Nilsson JA, Ahlborg HG, Karlsson MK. Bone mass following physical activity in young years: a mean 39-year prospective controlled study in men. Osteoporos Int. 2013; 24(4): 1389-1397.
22. Taaffe DR, Robinson TL, Snow CM, Marcus R. High-impact exercise promotes bone gain in well-trained female athletes. J Bone Miner Res. 1997; 12(2): 255-260.
23. Kudlac J, Nichols DL, Sanborn CF, DiMarco NM. Impact of detraining on bone loss in former collegiate female gymnasts. Calcif Tissue Int. 2004; 75(6): 482-487.
24. Friesen KJ, Rozenek R, Clippinger K, Gunter K, Russo AC, Sklar SE. Bone mineral density and body composition of collegiate modern dancers. J Dance Med Sci. 2011; 15(1): 31-36.
25. Mussolino ME, Looker AC, Orwoll ES. Jogging and bone mineral density in men: results from NHANES III. Am J Public Health. 2001; 91(7): 1056-1059.
26. Calbet JA, Moysi JS, Dorado C, Rodriguez LP. Bone mineral content and density in professional tennis players. Calcif Tissue Int. 1998; 62(6): 491-496.
27. Marks BL. Health benefits for veteran (senior) tennis players. Br J Sports Med. 2006; 40(5): 469-476.
28. Andreoli A, Monteleone M, Van Loan M, Promenzio L, Tarantino U, De Lorenzo A. Effects of different sports on bone density and muscle mass in highly trained athletes. Med Sci Sports Exerc. 2001; 33(4): 507-511.
29. Rebai H, Zarrouk N, Ghroubi S, Sellami M, Ayedi F, Baclouti S, Elleuch MH, Elleuch M. Long-term basketball playing enhances bone mass and isokinetic muscle strength. Isokinet Exerc Sci. 2012; 20(3): 221-227.
30. Alfredson H, Nordström P, Lorentzon R. Bone mass in female volleyball players: a comparison of total and regional bone mass in female volleyball players and nonactive females. Calcif Tissue Int. 1997; 60(4): 338-342.
31. Elloumi M, Courteix D, Sellami S, Tabka Z, Lac G. Bone mineral content and density of Tunisian male rugby players: differences between forwards and backs. Int J Sports Med. 2006; 27(5): 351-358.
32. Elloumi M, Ben Ounis O, Courteix D, Makni E, Sellami S, Tabka Z, Lac G. Long-term rugby practice enhances bone mass and metabolism in relation with physical fitness and playing position. J Bone Miner Metab. 2009; 27(6): 713-720.
33. Vincente-Rodrigues G, Dorado C, Perez-Gomez J, Gonzalez-Henriques JJ, Calbet JA. Enhanced bone mass and physical fitness in young female handball players. Bone. 2004; 35(5): 1208-1215.
34. Calbet JA, Dorado C, Díaz-Herrera P, Rodríguez--Rodríguez LP. High femoral bone mineral content and density in male football (soccer) players. Med Sci Sports Exerc. 2001; 33(10): 1682-1687.
35. Rittweger J, Beller G, Armbrecht G, Mulder E, Buehring B, Gast U, Dimeo F, Schubert H, de Haan A, Stegeman DF, Schiessl H, Felsenberg D. Prevention of bone loss during 56 days of strict bed rest by side-alternating resistive vibration exercise. Bone. 2010; 46(1): 137-147.
36. Santos A, Bakker AD, Klein-Nulend J. The role of osteocytes in bone mechanotransduction. Osteoporos Int. 2009; 20: 1027-1031.
37. Turner CH, Pavalko FM. Mechanotransduction and functional response of the skeleton to physical stress: the mechanisms and mechanics of bone adaptation. J Orthop Sci. 1998; 3(6): 346-355.
38. Bergmann P, Body JJ, Boonen S, Boutsen Y, Devogelaer JP, Goemaere S, Kaufman J, Reginster JY, Rozenberg S. Loading and skeletal development and maintenance. J Osteoporos. 2010; 2011: 786752.
39. Klein-Nulend J, van der Plas A, Semeins CM, Ajubi NE, Frangos JA, Nijweide PJ, Burger EH. Sensitivity of osteocytes to biomechanical stress in vitro. FASEB J. 1995; 9(5): 441-445.
40. Duncan RL, Turner CH. Mechanotransduction and the functional response of bone to mechanical strain. Calcif Tissue Int. 1995; 57(5): 344-358.
41. Frost HM. Why do marathon runners have less bone than weight lifters? A vital- biomechanical view and explanation. Bone. 1997; 20(3): 183-189.
42. Korpelainen R, Keinanen-Kiukaanniemi S, Heikkinen J, Vaananen K, Korpelainen J. Effect of impact exercise on bone mineral density in elderly women with low BMD: a population-based randomized controlled 30-month intervention. Osteoporos Int. 2006; 17: 109-118.
43. Zernicke R, MacKay C, Lorincz C. Mechanisms of bone remodeling during weight-bearing exercise. Appl Physiol Nutr Metab. 2006; 31(6): 655-660.
44. Skerry TM. One mechanostat or many? Modifications of the site-specific response of bone to mechanical loading by nature and nurture. J Musculoskelet Neuronal Interact. 2006; 6(2): 122-127.
45. Rubin CT, Lanyon LE. Regulation of bone mass by mechanical strain magnitude. Calcif Tissue Int. 1985; 37(4): 411-417.

46. Frost HM. Perspectives: a proposed general model for the "mechanostat" (suggestions from a new skeletal-biologic paradigm). Anat Rec. 1996; 244(2): 139-147.
47. Skerry TM. The response of bone to mechanical loading and disuse: fundamental principles and influences on osteoblast/osteocyte homeostasis. Arch Biochem Biophys. 2008; 473(2): 117-123.
48. Lanyon LE, Rubin CT. Static vs dynamic loads as an influence on bone remodelling. J Biomech. 1984; 17(12): 897-905.
49. Judex S, Gupta S, Rubin C. Regulation of mechanical signals in bone. Orthod Craniofac Res. 2009; 12(2): 94-104.
50. Turner CH, Owan I, Takano Y. Mechanotransduction in one: role of strain rate. Am J Physiol. 1995; 269, (3 Pt 1): E438-E442.
51. Robling AG, Hinant FM, Burr DB, Turner CH. Improved bone structure and strength after long-term mechanical loading is greatest if loading is separated into short bouts. J Bone Miner Res. 2002; 17(8): 1545-1554.
52. Ermin K, Owens S, Ford MA, Bass M. Bone mineral density of adolescent female tennis players and nontennis players. J Osteoporos. 2012; 1-5.
53. Etherington J, Harris PA, Nandra D, Hart DJ, Wolman RL, Doyle DV, Spector TD. The effect of weight-bearing exercise on bone mineral density: a study of female ex-elite athletes and general population. J Bone Miner Res. 1996; 11(9): 1333-1338.
54. Bolam KA, Van Uffelen JG, Taaffe DR. The effect of physical exercise on bone density in middle-aged and older men: a systematic review. Osteoporos Int. 2013; 24(11): 2749-2462.
55. Heinonen A, Oja P, Kannus P, Sievänen H, Haapasalo H, Mänttäri A, Vuori I. Bone mineral density of female athletes in different sports. Bone Miner. 1993; 23(1): 1-14.
56. Martyn-St James M, Carroll S. Effects of different impact exercise modalities on bone mineral density in premenopausal women: a meta-analysis. J Bone Miner Metab. 2010; 28(3): 251-267.
57. Vincent KR, Braith RW. Resistance exercise and bone turnover in elderly men and women. Med Sci Sports Exerc. 2002; 34(1): 17-23.
58. Heinonen A, Oja P, Kannus P, Sievänen H, Haapasalo H, Mänttäri A, Vuori I. Bone mineral density in female athletes representing sports with different loading characteristics of the skeleton. Bone. 1995; 17(3): 197-203.
59. Templeton DL, Kelly AS, Steinberger J, Dengel DR. Lower relative bone mineral content in obese adolescents: role of non-weight bearing exercise. Pediatr Exerc Sci. 2010; 22(4): 557-568.
60. Tenforde AS, Fredericson M. Influence of sports participation on bone health in the young athlete: a review of the literature. PM R. 2011; 3(9): 861-867.
61. Torstveit MK, Sundgot-Borgen J. Low bone mineral density is two to three times more prevalent in non-athletic premenopausal women than in elite athletes: a comprehensive controlled study. Br J Sports Med. 2005; 39(5): 282-287.
62. Haapasalo H, Kannus P, Sievänen H, Heinonen A, Oja P, Vuori I. Long-term unilateral loading and bone mineral density and content in female squash players. Calcif Tissue Int. 1994; 54(4): 249-255.
63. Sanchis-Moysi J, Dorado C, Olmedillas H, Serrano-Sanchez JA, Calbet JA. Bone and lean mass inter-arm asymmetries in young male tennis players depend on training frequency. Eur J Appl Physiol. 2010; 110(1): 83-90.
64. Alfredson H, Nordström P, Pietilä T, Lorentzon R. Long-term loading and regional bone mass of the arm in female volleyball players. Calcif Tissue Int. 1998; 62(4): 303-308.
65. Kannus P, Haapasalo H, Sankelo M, Sievänen H, Pasanen M, Heinonen A, Oja P, Vuori I. Effect of starting age of physical activity on bone mass in the dominant arm of tenis and squash players. Ann Intern Med. 1995; 123(1): 27-31.
66. Ireland A, Maden-Wilkinson T, Ganse B, Degens H, Rittweger J. Effects of age and starting age upon side asymmetry in the arms of veteran tennis players: a cross-sectional study. Osteoporos Int. 2014; 25(4): 1389-1400.
67. Nilsson M, Ohlsson C, Mellström D, Lorentzon M. Previous sport activity during childhood and adolescence is associated with increased cortical bone size in young adult men. J Bone Miner Res. 2009; 24(1): 125-133.
68. Nilsson M, Ohlsson C, Mellström D, Lorentzon M. Sport-specific association between exercise loading and the density, geometry, and microstructure of weight-bearing bone in young adult men. Osteoporos Int. 2013; 24(5): 1613-1622.
69. Kohrt WM, Barry DW, Schwartz RS. Muscle forces or gravity: what predominates mechanical loading on bone? Introduction. Med Sci Sports Exerc. 2009; 41(11): 2050-2055.
70. Yung PS, Lai YM, Tung PY, Tsui HT, Wong CK, Hung VW, Qin L. Effects of weight bearing and non-weight bearing exercises on bone properties using calcaneal quantitative ultrasound. Br J Sports Med. 2005; 39(8): 547-551.
71. Almstedt HC, Canepa JA, Ramirez DA, Shoepe TC. Changes in bone mineral density in response to 24 weeks of resistance training in college-age men and women. J Strength Cond Res. 2011; 25(4): 1098-1103.

72. Medelli J, Shabani M, Lounana J, Fardellone P, Campion F. Low bone mineral density and calcium intake in elite cyclists. J Sports Med Phys Fitness. 2009; 49(1): 44-53.
73. Rico H, Revilla M, Hernández ER, Gomez-Castresana F, Villa LF. Body mineral content and body composition in postpubertal cyclist boys. Bone. 1993; 14(2): 93-95.
74. Bilanin JE, Blanchard MS, Russek-Cohen E. Lower vertebral bone density in male long distance runners. Med Sci Sports Exerc. 1989; 21(1): 66-70.
75. Hetland ML, Haarbo J, Christiansen C. Low bone mass and high bone turnover in male long distance runners. J Clin Endocrinol Metab. 1993; 77(3): 770-775.
76. Gennari L, Merlotti D, Martini G, Gonnelli S, Franci B, Campagna S, Lucani B, Dal Canto N, Valenti R, Gennari C, Nuti R. Longitudinal association between sex hormone levels, bone loss, and bone turnover in elderly men. J Clin Endocrinol Metab. 2003; 88(11): 5327-5333.
77. Hackney AC, Styers AG. Recovery of the endocrine system following exercise. Med Sport. 1999; 3(3): 177-189.
78. Kraemer WJ, Patton JF, Gordon SE, Harman EA, Deschenes MR, Reynolds K, Newton RU, Triplett NT, Dziados JE. Compatibility of high-intensity strength and endurance training on hormonal and skeletal muscle adaptations. J Appl Physiol. 1995; 78(3): 976-989.
79. Yingling VR, Davies S, Silva MJ. The effects of repetitive physiologic loading on bone turnover and mechanical properties in adult female and male rats. Calcif Tissue Int. 2001; 68(4): 235-239.
80. Boudreaux RD, Swiff JM, Gasier HG, Wiggs MP, Hogan HA, Fluckey JD, Bloomfield SA. Increased resistance during jump exercise does not enhance cortical bone formation. Med Sci Sports Exerc. 2014; 46(5): 982-989.
81. Villareal DT, Shah K, Banks MR, Sinacore DR, Klein S. Effect of weight loss and exercise therapy on bone metabolism and mass in obese older adults: a one-year randomized controlled trial. J Clin Endocrinol Metab. 2008; 93(6): 2181-2187.
82. Jensen LB, Quaade F, Sørensen OH. Bone loss accompanying voluntary weight loss in obese humans. J Bone Miner Res. 1994; 9(4): 459-463.
83. De Souza MJ, Nattiv A, Joy E, Misra M, Williams NI, Mallinson RJ, Gibbs JC, Olmsted M, Goolsby M, Matheson G. Expert Panel. 2014 Female Athlete Triad Coalition Consensus Statement on Treatment and Return to Play of the Female Athlete Triad: 1st International Conference held in San Francisco, California, May 2012 and 2nd International Conference held in Indianapolis, Indiana, May 2013. Br J Sports Med. 2014; 48(4): 289.
84. De Souza MJ, West SL, Jamal SA, Hawker GA, Gundberg CM, Williams NI. The presence of both an energy deficiency and estrogen deficiency exacerbate alterations of bone metabolism in exercising women. Bone. 2008; 43: 140-148.
85. Duckham RL, Peirce N, Meyer C, Summers GD, Cameron N, Brooke-Wavell K. Risk factors for stress fracture in female endurance athletes: a cross-sectional study. BMJ Open. 2012; 2(6): e001920.
86. Barrack MT, Gibbs JC, De Souza MJ, Williams NI, Nicholas JF, Rauh MJ, Nattiv A. Higher incidence of bone stress injury with increasing female athlete triad risk factors: a prospective multisite study of exercising girls and women. Am J Sports Med. 2014; 42(4): 949-958.
87. Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR. Physical activity and bone health. Med Sci Sports Exerc. 2004; 36(11): 1985-1996.
88. Dawson-Hughes B. 70th Anniversary conference on: vitamins in early development and healthy aging: impact on infectious and chronic disease. Symposium 1: vitamins and cognitive development and performance serum 25-hydroxyvitamin D and muscle atrophy in the elderly. P Nutr Soc. 2012; 71(1): 46-49.
89. Holick MF. Vitamin D: a millenium perspective. J Cell Biochem. 2003; 88: 296-307.
90. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004; 80: 1678S-1688S.
91. Jones KS, Assar S, Vandetschueren D, Bouillon R, Prentice A, Schoenmakers I. Predictors of 25(OH)D hal-life and plasma 25(OH)D concentration in The Gambia and UK. Osteoporos Int. 2015; 26: 1137-1146.
92. Adorini L. Immunomodulatory effects of vitamin D receptor ligands in autoimmune diseases. Int Immunopharmacol. 2002; 2: 1017-1028.
93. Haussler MR, Jurutka PW, Hsieh JC, Thompson PD, Selznick SH, Haussler CA, Whitfield GK. New understanding of the molecular mechanism of receptor-mediatel genomie action of the vitamin D hormone. Bone. 1995; 17: 33S-38S.
94. Płudowski P, Grant WB, Bhattoa HP, Bayer M, Povoroznyuk V, Rudenka E, Ramanau H, Varbiro S, Rudenka A, Karczmarewicz E, Lorenc R, Czech-Kowalska J, Konstantynowicz J. Vitamin D status in Central Europe. Int J Endocrinol. 2014; ID: 589587: 1-12.
95. Campbell PMF, Allain TJ. Muscle strength and vitamin D in older people. Gerontology. 2006; 52: 335-338.
96. Marantes I, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ 3rd, Amin S. Is vitamin D a determinant of muscle mass and strength? J Bone Miner Res. 2011; 26: 2860-2871.

97. Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. Calcif Tissue Int. 2013; 92: 151-162.
98. Wacker M, Holick MF. Vitamin D – effects on skeletal and extraskeletal health and the need for supplementation. Nutrients. 2013; 5: 111-148.
99. Sinha A, Hollingsworth KG, Ball S, Cheetham T. Improving the vitamin D status of vitamin D deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle. J Clin Endocrinol Metab. 2013; 98: E509-E513.
100. Garcia LA, King KK, Ferrini MG, Norris KC, Artaza JN. 1,25$(OH)_2$ vitamin 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.
101. Webb AR, Holick MF. The role of sunlight in the cutaneous production of vitamin D3. Annu Rev Nutr. 1988; 8: 375-399.
102. Guillemant J, Le HT, Maria A, Allemandou A, Pérès G, Guillemant S. Wintertime vitamin D deficiency in male adolescents: effect on parathyroid function and response to vitamin D3 supplements. Osteoporos Int. 2001; 12(10): 875-879.
103. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000; 72(3): 690-693.
104. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357(3): 266-281.
105. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ. 2009; 339(7725): 843-846.
106. Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis. Q J Med. 2007; 100(4): 185-192.
107. Nagpal S, Na S, Rathnachalam R. Noncalcemic action of vitamin D receptor ligands. Endocr Rev. 2005; 26: 662-687.
108. Rejnmark L. Effects of vitamin D on muscle function and performance: A review of evidence from randomized controlled trials. Ther Adv Chronic Dis. 2011; 2(1): 25-37.
109. Grimaldi AS, Parker BA, Capizzi JA, Clarkson PM, Pescatello LS, White MC, Thompson PD. 25(OH) vitamin D is associated with greater muscle strength in healthy men and women. Med Sci Sports Exerc. 2013; 45(1): 157-162.
110. Sato Y, Inose M, Higuchi I, Higuchi F, Kondo I. Changes in the supporting muscles of the fractured hip in elderly women. Bone. 2002; 30(1): 325-330.
111. Snijder MB, van Dam RM, Visser M, Deeg DJ, Dekker JM, Bouter LM, Seidell JC, Lips P. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. J Clin Endocrinol Metab. 2005; 90(7): 4119--4123.
112. Hamilton B, Grantham J, Racinais S, Chalabi H. Vitamin D deficiency is endemic in Middle Eastern sportsmen. Public Health Nutr. 2010; 13(10): 1528-1534.
113. Lovell G. Vitamin D status of females in an elite gymnastics program. Clin J Sport Med. 2008; 18: 159-161.
114. Constantini NW, Arieli R, Chodick G, Dubnov-Raz G. High prevalence of vitamin D insufficiency in athletes and dancers. Clin J Sport Med. 2010; 20(5): 368-371.
115. Hamilton B. Vitamin D and athletic performance: The potential role of muscle. Asian J Sports Med. 2011; 2(4): 211-219.
116. Willis KS, Peterson J, Larson-Meyer DE. Should we be concerned about the vitamin D status of athletes? Int J Sport Nutr Exerc Metab. 2008; 18: 204-224.
117. Close GL, Russell J, Cobley JN, Owens DJ, Wilson G, Gregson W, Fraser WD, Morton JP. Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. J Sports Sci. 2013; 31(4): 344-353.