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Research article

Osteoporosis and sport

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ABSTRACT

Osteoporosis is common throughout the world. Complications include fragility fractures. In this paper I will describe the condition as it relates to athletes young and old. It will be seen that osteoporosis may result from poorly managed sporting activities at the same time it may be ameliorated by exercise in those susceptible to the disorder.

I will discuss the epidemiology, the protective effect of exercise, the therapeutic benefits of sport and exercise in the older population with fragility fractures, the effects of weight limited sport and the severe risks to those who diet and exercise intensely at the same time. I will cover the range of diagnostic investigations including imaging and non-radiological techniques and focus on advice to the coach and athlete to maintain bone health throughout an athletic and sporting lifetime.

1. Introduction

Every human being is affected by osteoporosis if they live long enough. We reach our peak bone mineral density around 20 years of age and this steadily falls by around 1% per year thereafter. The average 80-year-old may have 40% of their original bone mineral. Some lose bone mineral faster. If they reach 25% or less of their maximum bone mineral then spontaneous fractures may occur with no or minimal trauma [1]. Those involved in sport are naturally affected by the same process.

Fractures of the spine, hips or forearm are common complications of osteoporosis and may have life changing or life limiting consequences. Around 8.9 million fractures a year occur worldwide resulting from osteoporosis [2]. After a fracture that might be associated with bone fragility there is a statistically increased risk of subsequent fractures between 60 and 82 per 10,000 patient years [3].

It has been argued that exercise may offset, delay or mitigate the effects of osteoporosis [4].

Factors that accelerate bone loss are a genetic predisposition, maternal history of hip fracture, the use of steroids for any purpose [5], lack of dietary calcium, insufficient vitamin D, systemic illness, absorption disorders, treatment with aromatase inhibitors (for breast cancer), renal disease, smoking, heparin and oral anticoagulant administration, prolonged immobilisation, hyperparathyroidism, hyperthyroidism, diabetes mellitus, high alcohol use and deliberate weight loss especially with a body mass index of less than 20 kg/m^2.

The issues that are specific to sport are use and abuse of steroids and deliberate restriction in nutrition to achieve weight targets and dieting goals.

In this paper I will consider the epidemiology of osteoporosis, its damaging effects in the short-term and long-term along with its influence on longevity and how a sporting career may be harmed.

2. Definitions of osteoporosis

The World Health Organisation in 1994 defined osteopenia and osteoporosis as:-

- normal (T-score -1.0 and above)
- low bone mass, referred to as osteopenia (T-score between -1.0 and -2.5)
- osteoporosis (T-score -2.5 and below)
- severe osteoporosis (T-score -2.5 and below with history of a fracture)

These criteria apply only to white postmenopausal women as the research data was primarily limited to this group. The diagnosis can only be made from measurements at three sites, lumbar spine, hip or forearm [2].

In 2008 the outcome of a WHO study group was published. It noted that DEXA examination has a high specificity for osteoporosis but low sensitivity. It commented that there was little evidence that osteoporosis can be usefully tackled by public health policies including smoking exercise and nutrition. They discussed the need for screening

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particularly in high risk individuals [6]

3. Epidemiology

3.1. Genetic factors

Family history has a strong association with accelerated mineral loss from bone. There is a much higher incidence in particular racial groups although the influence of the amount of light and dietary calcium has an impact mixed with genetic tendencies. For example, those most commonly affected by selective axial osteoporosis, with relative sparing of the extremities tend to be of Scandinavian ancestry. Of course, these individuals also tend to live in countries with less ambient light. Conversely those of Scandinavian background often have a higher intake of dairy products and therefore are at lower risk of calcium deficiency. Populations with lactose intolerance have the opposite problem [7].

3.2. Steroids

A short course of oral steroids is commonly used in young people with severe asthma. This includes those with exercise induce asthma. The effect on bone mineral is duration and dose related but even a short course may adversely affect bone health [5]. The mechanisms are through a variety of effects on both osteoblast and osteoclast activity. The effects are dose-related and are seen within 3–6 months of starting the medication. Fracture risk increases during treatment and declines after withdrawal but probably does not return to baseline. Once bone density takes a step wise reduction it is hard to reverse the process.

Anabolic steroids taken to enhance performance also have lasting damaging effects and their use is unlikely to be documented, controlled or monitored.

3.3. Obesity

Current data suggest that with obesity and high BMI indices there is an increased risk of some fractures such as lower limb and proximal humerus but there may be some protection in others including hip and wrist. Bone mineral density tends to be higher with obesity but it may not be sufficient to mitigate the greater forces involved in obese patients when they fall [8].

3.4. Deliberate weight loss

In an attempt to "level the playing field" for those of lower stature many sports where size is critical set weight limit restrictions. Common examples are the martial arts, rowing [9], distance running [10] and horse racing (jockeys). There are also a group of slimmers who use endurance exercise as well as diet and can become obsessed by the process to the detriment of their health. This is more common in women and is termed the "female athlete triad" (menstrual dysfunction, low energy and decreased bone mineral density) [11] Fig. 1. Inevitably those who are naturally a lightweight will be less competitive than those who slim down to the required weight as the latter is likely to be taller with longer levers. It is common in weight-based events for the competitors all to be naturally considerably heavier than the category in which they are competing. In women this deliberate weight loss may lead to amenorrhoea and even vertebral insufficiency fractures Fig. 2. The need to make a target weight means that many will be dehydrated at the time of the weigh in, as this is often several hours or a day earlier than the event. It is common for those competing to be over the weight limit at the time of the event. The loss of weight and reaching targets becomes an obsession in those involved in lightweight competition. In addition, the level at which the maximum or average team weight is set will effectively include a small subset of athletes who are large enough to be effective but small enough to be able to slim down to the required limit. Altering the weight limit by a few kilograms would exclude certain individuals whilst including a group of others. It is naïve to imagine that a weight threshold includes all those under that weight. In practice a weight category, only includes a thin band of those naturally above the weight limit. Unfortunately, competitive athletes rarely think ahead to their middle or later years and many involved in these competitions have not understood or appreciated the potential long-term morbidity.

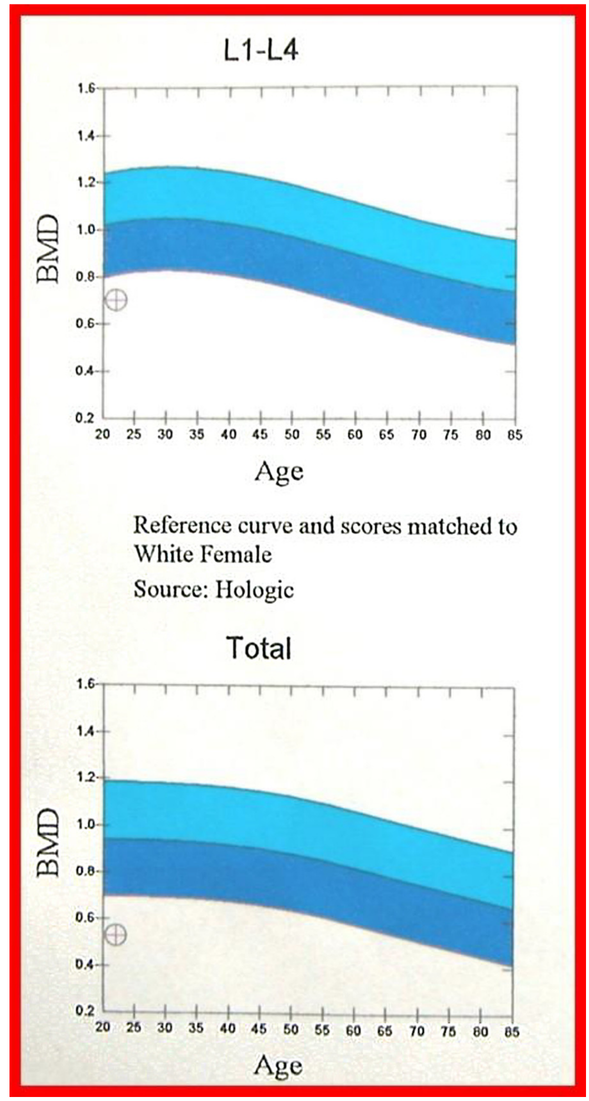

Fig. 1. DEXA examination of an elite lightweight female rower aged 21. Considerably below normal measurements for lumbar spine and left hip.

There are examples of how exercise can increase bone density and it may be that diet is the crucial factor where the coach and athlete should concentrate [12].

4. Preventative effects of exercise

It has long been held that exercise increases the strength of bone. There is evidence in soldiers undergoing even a short period of exercise that this is the case [13]. Regular Tai Chi Chuan would appear to be of benefit [14].

Studies have shown that high-intensity progressive resistance training may increase vertical height and femoral neck bone mineral density. There is also evidence that low impact exercise such as walking may reduce bone resorption [15]. Whether these factors outweigh the common deleterious effects of ageing, alcohol and smoking is in question. Although difficult to quantify it would seem that exercise may be

Fig. 2. Vertebral compression fracture in a 25 year old who used dieting and endurance running to “keep her weight normal”.

helpful but probably cannot be relied upon as a primary treatment. There is research underway that may reveal more, for example the study of resistance and balance exercise for women with vertebral fractures associated with osteoporosis [16]. A Cochrane review concluded that the most effective exercise to improve bone mineral density in the femoral neck appears to be non-weightbearing high force exercise such as resistance strength training for the lower limbs. For the spine a combination exercise program seems most beneficial [17]. However, this review also commented that the beneficial effects on bone mineral density are relatively small. This is important as those who attempt to lose weight and exercise intensely may reduce their bone mineral density more from the dieting and weight loss than they gain from the exercise. In a study from the University of Arizona the exercises that increased the bone mineral density the most were squat, military, back extension, pull down, and seated row [18]. Some evidence suggests that in women a combination of hormone replacement therapy plus exercise is more effective than hormone replacement alone [19].

There is evidence that exercise improves function and mobility in patients diagnosed as suffering from osteoporosis. This meta-analysis encompasses patients with osteoporosis without specifically studying those with fractures alone. What is probably self-evident is that all the people become more mobile and function better and it is reassuring that this applies to those with osteoporosis [20].

5. Methods of assessment [21–23]

There are a variety of techniques employed in the diagnosis of osteoporosis which otherwise tends to be an occult disease [22].

5.1. Body mass index

The simplest approach is to use a body mass index (BMI) derived from weight and height. This method can give erroneous figures in athletes who have large, heavy muscle bulk. The thresholds of overweight (BMI 25 +) and obesity (BMI 30 +) may be exceeded by athletes with a mesomorphic habitus or those who train to increase muscle bulk. BMI thresholds can be corrected for these body types.

5.2. Whole body DEXA

Whole body fat content can be measures by DEXA.

5.3. Bone mineral DEXA

DEXA (Dual Energy X-Ray Absorptiometry) was originally developed to measure bone mineral. The differential absorption of x-ray by bone is measured at two energy levels. Normal data from large numbers of volunteers are used to calculate the amount of calcium in the lumbar spine and / or the hip. The results may be confused by advance degenerative disease and by previous fractures. The hip bone density does not always correlate with measurements from the spine. There are inherited elements to the disease that can cause selective axial osteoporosis. Perhaps the greatest problem with this method is the lack of association between dense bone and strong bone. The causes of fragility and tendency to fracture are not a simple matter. Coarsening of the trabecular pattern with micro fenestrations in the trabeculae are almost certainly a major factor in fracture causation and are not measured by DEXA. The radiation doses involved are tiny, sufficiently low to allow the operator to reasonably sit next to the machine and are not a practical consideration.

5.4. Transmission ultrasound

The bone mineral content although related to bone fragility does not take into account the trabecular structure of bone. If we imagine a long bone such as the femur completely ossified with no trabecular cavities it would be heavy, strong for compression loading but very brittle and subject to fracture by transverse or bending forces. It might be likened to a stick of Blackpool rock, very hard but liable to smash if you hit it. The trabecular structure of bone provides elasticity and reduces the weight. A normal femur is light and can bend before it breaks. In osteoporosis not only is there mineral loss but also coarsening of the trabecular structure. Ultrasound techniques include quantitative ultrasound based on the velocity of sound through the bone, and ultrasound attenuation. Transmission Ultrasound or reflected ultrasound beams may be used to measure the quality of trabecular structure by how much the bone attenuates the sound beam [24]. There is commercial apparatus which uses ultrasound transmitted through a bone such as the calcaneus to measure its quality. Unfortunately, this is impractical in the spine where some of the most serious fractures occur and the frequency of the ultrasound beam is too high to achieve the penetration that would be required to measure the hip. An alternative strategy is to use a reflected beam of ultrasound and work is in progress to expand the use of this new technology.

5.5. Quantitative computed tomography

Conventional CT examinations generate a picture of bone and equipment of sufficient resolution can show the course elements of trabecular structure. The attenuation of the x-ray beam is a measure of the density of bone but also takes into account the number of holes within the sub cortical bone. It allows measurement to exclude cortical bone and is arguably a better measure of bone quality. Calibrating the image using standardised concentrations of calcium in a phantom or more recently on newer machines by software techniques allows the use of conventional x-ray images of the spine and other bones to be used to measure the amount of mineral in a given area of bone. The disadvantage of this technique is that It uses ionising radiation of considerably higher dose than DEXA and somewhat higher than conventional radiographs. Adaptation of cone beam CT and new software packages of conventional CT are reducing the radiation involved in making this technique more practical.

5.6. MRI densitometry

Magnetic resonance imaging uses the water content of the body to create images. Proton density sequences homogenise differences in marrow composition and provided that a porosity phantom is used for calibration, software can analyse the image to measure both bone density and cross section geometric properties. Studies have shown that there is a strong correlation between MRI densitometry, quantitative CT and the reference standard of ash density. The standard is derived from experimental data where a bone is examined and then burnt to create ash from which the quantity of mineral can be directly measured.

Despite widespread application of the techniques described above there remains some doubt that we are truly measuring the strength of bone. Techniques that measure mineral content only ignore the structural strength rated by trabeculae. Techniques that measure trabecular pattern may not include an index of the mineral content. Current research suggests that the quality of trabecular pattern including holes within the trabecular walls created by osteoclasts, a process sometimes termed fenestration, maybe a more important measure of bone strength than mineral content alone. What this means in practice is that some patients with borderline bone mineral density measurements may have relatively strong bone whilst others fracture more easily than would be expected from their mineral density measurements. The most commonly used measure of bone mineral is DEXA and the above issues mean that we should not rely entirely on this index to predict the patient's risk.

5.7. Risk scoring

The team at the University of Sheffield (https://www.sheffield.ac.uk/FRAX/) have developed online software that allows prediction of fracture risk without the need for bone mineral density measurements or measure of trabecular strength [25]. They use the individual's gender and history to predict fractures and using the online application any person or their healthcare practitioner can obtain a prediction of fracture risk. Including results of DEXA examination improves the statistics. A DEXA examination result may be used to improve the precision but is not essential [26].

The Garvan calculator has been developed in Sydney Australia and this includes the number of falls (https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/).

The scoring techniques are easy to apply and may identify those needing prophylactic therapy [27].

5.8. Bone turnover markers

Collagen degradation products such as βCTX are released during bone resorption and may be a measure of osteoclast activity. Bone formation markers such as PINP and PICP are measures of osteoblast activity. The International Osteoporosis Foundation recommends the use of these markers although there are only limited clinical trials regarding their efficacy [28].

6. Stress lesions in bone

Stress injuries of bone are common in sporting activity. They may be defined as microfractures occurring in bone due to repetitive use by the forces involved that exceed the strength of that bone, and repair processes do not deal with the remodelling required to maintain integrity. The fractures occurring at a microscopic level may progress to more extensive fracturing and eventually complete failure of the bone with a stress fracture. Typically, the repair processes that are triggered by the initial injury create sclerosis and oedema which may be identified on imaging.

The most sensitive techniques for detecting stress lesions are magnetic resonance imaging to identify oedema of bone, single photon emission computed tomography (SPECT) to detect increased metabolic activity at the injury site, and conventional computed tomography to identify areas of sclerosis and fracture lines. Conventional radiographs are much less sensitive to these processes but will show sclerosis, localised periosteal reaction and fractures when they occur.

Stress injuries of bone may occur in people with normal bone density and bone strength if the forces are repetitive and strong. It is likely that those involved in competitive sport that involves multiple repetitions gradually build up and improve strength in the affected bones and this will prevent the occurrence of stress injury and stress fracture. However, individuals with reduced bone strength will not adapt as well. Stress injuries are much more common in individuals with osteopenia or osteoporosis.

It might be argued that the stress injury of bone and more advanced age stress fractures of bone are always insufficiency fractures. In the athlete with normal bone, when compared to someone who does not take part in a sport the bone strength may be insufficient for the forces applied by the repetitive activity involved in sport [29]. This is to say that sport requires stronger bone in particular locations than the average normal individual. Someone with severe osteoporosis may fracture the hip or the spine during normal daily activity but they may also develop a stress response before the bone collapses completely. The mechanisms of partial repair and bone collapse are the same as seen in the athlete with normal bone strength and the older individual with osteoporosis.

When stress lesions are identified proper management is to reduce the level of stress thus allowing the bone to heal normally and remodel with this strengthened structure. In practice this is much more difficult with highly motivated athletes. Frequently, despite careful explanation and instruction the athlete will ignore advice and continue in sporting activity leading to a full fracture. This is a matter of education not only for the athlete but also the coach and in younger athletes the parents. The process of unloading and then re-establishing training regimes is very effective in dealing with this problem but very hard to achieve.

7. The ageing athlete

Athletic and sporting activity is now commonplace in the older population. Masters sport is very popular and there is a significant probability that individuals with conventional osteopenia and osteoporosis will be taking part in sporting activities. Coaches and medical advisers will need to take into account training patterns, frequency of activity and the athletes bone mineral and bone strength. Different sports involve different risks. Endurance activities, especially long-distance running, are popular in the older age groups partly because they do not involve impact and also because the older athlete will have lost muscle bulk and will be more effective at endurance activity than they would be at explosive or short duration exercise. This means that the repetitive stress on bone will be higher for the older athlete.

8. Treatment of osteoporosis [30]

Medical treatment for osteoporosis and osteopenia centres around restoring bone mineral density [31]. Adequate calcium intake and sufficient vitamin D are essential for normal bone health. In the average size adult this is the equivalent to 500 mL of milk or other dairy products per day. Note that low-fat dairy products often have slightly higher calcium content than those with higher levels of fat. Those with lactose intolerance will have a particular problem in maintaining adequate calcium intake and individuals who choose a strict vegan diet may be similarly compromised. In these circumstances, calcium supplements may be recommended even for those who are not at an age where osteoporosis might be expected. Vitamin D levels are endemically low in those living in the northern parts of Europe because of the lack of sunlight. This is worse in those with dark skin. Approximately 3 ½ hours per day of exposure to sunlight on the arms, neck and face are required to maintain an adequate vitamin D level. In practice this means that most people living in a country like the United Kingdom or Scandinavia will be vitamin D deficient. Supplements of vitamin D are easy to obtain and a dose of 1000 International units (25 μg) per day will suffice. It has been proposed that 3000 International units (75 μg) per day would be preferred but consensus is currently for the lower dose. It should be noted that combined vitamin D and calcium preparations often contain a much lower dose of vitamin D probably insufficient to deal with the common deficiencies. This is because approval for these agents was obtained before knowledge of the advantage of the higher 1000 International unit dose and it is unlikely that pharmaceutical companies would seek to re-validate a different formulation because of the costs involved. In practice this means that is prudent to separate the administration of calcium and vitamin D avoiding combination preparations.

Those with established osteoporosis are likely to be treated with bisphosphonates or other antiresorptive drugs. Those with severe spinal osteoporosis and fractures might be given daily subcutaneous injections of Teriparatide as it is recorded as having a better effect on spinal mineralisation [30]. Most of these agents work by reducing osteoclast activity allowing relative positive balance of osteoblastic activity. Unfortunately, this does not assist with bone microstructure and the trabeculae may remain abnormal and weakened. The evidence on whether bisphosphonate reduces fracture risk is based on large studies of fracture rates in the treated and untreated groups. However, countering this supportive data, bisphosphonate medication may lead to excessive mineralisation of bone turning the long bones into hard and therefore brittle structures. This is why atypical fractures of the femur may occur in patients who have been treated with antiresorptive agents. These problems apply to bisphosphonates and the rank ligand inhibitor agents like Denusomab. Athletes on treatment with such drugs are at potential risk from shear forces applied to the long bones. Fortunately, the statistics suggest that the benefits of medication to reverse bone mineral loss outweigh the disadvantages. The risk of osteonecrosis of the jaw is around 0.4 cases per 10,000 patient years and the risk of atypical fractures is between five and 100 per 100,000 patient years [30].

9. Conclusions

- Osteoporosis and its precursor osteopenia are common in the ageing population who may be involved in athletic activity.
- Abnormal bone mineral and reduced bone strength may occur in younger athletes who are competing in weight band sports as there is competitive advantage in being larger in body frame and reducing the weight by heavy dieting.
- Vitamin D deficiency is common in northern countries due to lack of exposure to sunlight.
- Inadequate calcium intake is common in those on a strict diet or those with lactose intolerance.
- There are small benefits to bone mineral density from impact exercise, however those who diet and use intense endurance exercise to lose weight may have a damaging effect on their bone mineral density.
- Stress injuries of bone are much more likely in those with reduced bone mineral density or reduced bone strength.
- Abuse of performance enhancing drugs, in particular anabolic steroids may induce osteoporosis.

Coaches and athletes should be aware of these risks and take preventative measures. Exercise should be encouraged in all age groups including those affected by osteoporosis.

References

[1] Gauthier, A., et al., Epidemiological burden of postmenopausal osteoporosis in the UK from 2010 to 2021: estimations from a disease model. 2011. 6(1): p. 179-188.
[2] A.S. Cruz, et al., Artificial intelligence on the identification of risk groups for osteoporosis, a general review, Biomed. Eng. Online 17 (1) (2018) 12.
[3] R.Y. van der Velde, et al., Incidence of Subsequent Fractures in the UK Between 1990 and 2012 Among Individuals 50 Years or Older, (2018).
[4] J.A. Fletcher, Canadian Academy of Sport and Exercise Medicine position statement: osteoporosis and exercise, Clin. J. Sport Med. 23 (5) (2013) 333–338.
[5] J. Compston, Glucocorticoid-induced osteoporosis: an update, Endocrine 61 (1) (2018) 7–16.
[6] J.A. Kanis, J.A.J.O.I. Kanis, Assessment of fracture risk and its application to screening for postmenopausal osteoporosis, Synopsis of a WHO report 4 (6) (1994) 368–381.
[7] J. Hippisley-Cox, C. Coupland, Predicting Risk of Osteoporotic Fracture in Men and Women in England and Wales: Prospective Derivation and Validation of QFractureScores, (2009), p. 339.
[8] A. Fassio, et al., The obesity paradox and osteoporosis, Eat. Weight Disord. 23 (3) (2018) 293–302.
[9] L. Dimitriou, et al., Bone mineral density, rib pain and other features of the female athlete triad in elite lightweight rowers, BMJ Open 4 (2) (2014).
[10] H. Brahm, et al., Bone metabolism in endurance trained athletes: a comparison to population-based controls based on DXA, SXA, quantitative ultrasound, and biochemical markers, Calcif. Tissue Int. 61 (6) (1997) 448–454.
[11] T.G. Nazem, K.E. Ackerman, The female athlete triad, Sport. Health A Multidiscip. Approach 4 (4) (2012) 302–311.
[12] K.J. Mackelvie, et al., Bone mineral density and serum testosterone in chronically trained, high mileage 40–55 year old male runners, Br. J. Sports Med. 34 (4) (2000) 273.
[13] Eleftheriou, K.I., et al., The Lichfield bone study: the skeletal response to exercise in healthy young men. 2012. 112(4): p. 615-626.
[14] T.H. Chow, et al., The effect of Chinese martial arts Tai Chi Chuan on prevention of osteoporosis: a systematic review, J. Orthop. Translat. 12 (2018) 74–84.
[15] H. Senderovich, A. Kosmopoulos, An insight into the effect of exercises on the prevention of osteoporosis and associated fractures in high-risk individuals, Rambam Maimonides Med. J. 9 (2018).
[16] B. Stanghelle, et al., Effect of a resistance and balance exercise programme for women with osteoporosis and vertebral fracture: study protocol for a randomized

controlled trial, BMC Musculoskelet. Disord. 19 (1) (2018) 100.
[17] T.E. Howe, et al., Exercise for preventing and treating osteoporosis in postmenopausal women, Cochrane Database Syst. Rev. (7) (2011) CD000333.
[18] L.B. Houtkooper, et al., Preventing osteoporosis the bone estrogen strength training way, ACSMs Health Fit. J. 11 (1) (2007) 21–27.
[19] D.T. Villareal, et al., Effects of exercise training added to ongoing hormone replacement therapy on bone mineral density in frail elderly women, J. Am. Geriatr. Soc. 51 (7) (2003) 985–990.
[20] A. Varahra, et al., Exercise to improve functional outcomes in persons with osteoporosis: a systematic review and meta-analysis, Osteoporos. Int. 29 (2) (2018) 265–286.
[21] S. Guerri, et al., Quantitative imaging techniques for the assessment of osteoporosis and sarcopenia, Quant. Imaging Med. Surg. 8 (1) (2018) 60–85.
[22] P. Choksi, K.J. Jepsen, G.A. Clines, The challenges of diagnosing osteoporosis and the limitations of currently available tools, Clin. Diabetes Endocrinol. 4 (2018) 12.
[23] Kanis, J.A., et al., European guidance for the diagnosis and management of osteoporosis in postmenopausal women. 2013. 24(1): p. 23-57.
[24] M.L. Frost, G.M. Blake, I. Fogelman, Can the WHO criteria for diagnosing osteoporosis be applied to calcaneal quantitative ultrasound? Osteoporos. Int. 11 (4) (2000) 321–330.
[25] E. Franek, et al., WHO fracture risk calculator (FRAX) in the assessment of obese patients with osteoporosis, Endokrynol. Pol. 60 (2) (2009) 82–87.
[26] T.A. Hillier, et al., WHO absolute fracture risk models (FRAX): do clinical risk factors improve fracture prediction in older women without osteoporosis? J. Bone Miner. Res. 26 (8) (2011) 1774–1782.
[27] S.L. Silverman, B.S. Komm, S. Mirkin, Use of FRAX(R)-based fracture risk assessments to identify patients who will benefit from osteoporosis therapy, Maturitas 79 (3) (2014) 241–247.
[28] P. Glendenning, Markers of Bone Turnover for the Prediction of Fracture Risk and Monitoring of Osteoporosis Treatment: A Need for International Reference Standards, Osteoporos. Int. 22 (2011) 391–420. The Clinical Biochemist Reviews, 2011. **32**(1): p. 45-47.
[29] Barrack, M.T., et al., Higher incidence of bone stress injuries with increasing female athlete triad–Related risk factors: A Prospective Multisite Study of Exercising Girls and Women. 2014. 42(4): p. 949-958.
[30] X. Nogues, D. Martinez-Laguna, Update on osteoporosis treatment, Med. Clin. (Barc) 150 (12) (2018) 479–486.
[31] H. Awasthi, et al., The underlying pathophysiology and therapeutic approaches for osteoporosis, Med. Res. Rev. (2018).