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Osteoporosis in Female Athletes

Review Article

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Abstract

Osteoporosis afflicts millions of women worldwide, but is especially prevalent among female athletes. The stress of intense workouts places these female athletes at a greater risk than the general female population. Absence or suppression of menstruation in female athletes leads to a low peak bone mass and subsequently to the weakening of their bones. This domino effect, coupled with their participation in physical activities, greatly amplifies their susceptibility to stress fractures. Although intense workouts cannot be removed from the regimen of female athletes, increased awareness may prevent or lessen the effects of osteoporosis. Enlightening female athletes on the importance of screening and the methods of diagnosing and treating this condition is the focus of this review.

Keywords: Bone; Bone Mass Density; Osteoporosis; Amenorrhea; Sports; Female Athletes.

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Introduction

Osteoporosis is a condition that affects almost 10 per-cent of the total female population worldwide and is especially prevalent among female athletes. This dis-ease is characterized by a decrease in bone mass and density and enlargement of bone spaces producing po-rosity and fragility. With the number of women of all ages participating in physical activity steadily increas-ing, the relationship between osteoporosis and female athletes is a growing concern [1-4]. It is estimated that more than 6 million women now compete in strenuous exercise, worldwide. Despite the benefits of exercise, excessive and strenuous physical activity can have neg-ative effects on the reproductive and skeletal systems, leading to osteoporosis [5,6]

Anatomy And Physiology

The skeleton, comprised of bone attached with vari-ous connective tissues, provides the vehicle with which the body can perform its daily tasks. The skeletal sys-tem has many functions; it supports and maintains the framework of the body, aids in body movement, pro-tects internal vital organs, and acts as a mineral res-ervoir[7,8]. An integral part of the skeletal system is bone. Bone is a dynamic structure, composed of an organic framework embedded in an inorganic salt [7]. This organic framework is 80% cortical (compact) bone that provides rigidity and tensility; the strength and elasticity come from 20% of trabecular (cancel-lous) bones[7-11].

Bone is dynamically involved in a continuous process of formation and resorption, known as the bone re-modeling process [8,10,12,13]. This process is per-formed by bone remodeling units and basic multicel-lular units (BMU) [14]. There are two types of cells associated with bone - osteoclasts and osteoblasts. Osteoclasts are involved with bone resorption, whereas osteoblasts are involved with bone formation. Bone remodeling is initiated by the osteoclast [15]. Osteo-clasts contain enzymes that infiltrate the bone surface.

When these enzymes are activated, they dissolve the bone surface, forming small erosion lacunae, which contain the osteocyte cells, releasing the inorganic salts [8,16]. Osteoblasts produce proteins of the bone ma-trix and regulate the rate of bone turnover and forma-tion. Osteoblasts secrete osteoid, the bone matrix [8,10,16] and osteogenin initiates and promotes osteo-genesis [16]. The newly formed matrix mineralizes in a span of three months, completing the bone formation process [8]. After reaching maximum bone mass, the bone remodeling process becomes uncoupled. This uncoupling process results in net loss of bone mass density which may lead to osteoporosis [15,17-20].

In female athletes, there is a higher incidence of osteo-porosis due to a lower rate of bone accretion, leading to a lower peak bone mass, particularly in athletes with delayed menarche [5]. Studies have reported a lower vertebral Bone Mass Density (BMD) among young amenorrheic athletes than among athletes with regular cycles [21].

Pathophysiology

Osteopenia is reduction in bone volume to below nor-mal levels

due to inadequate replacement of bone lost to normal lysis. Hyperprolactinemia, excessive exer-cise, stress, under nutrition, and anorexia nervosa are all causes of functional acquired gonadotrophin releas-ing hormone (GnRH) deficiency and are associated with osteopenia [22]. The common pathophysiology observed in most cases is hypo-oestrogenism due to suppression of the GnRH pulse generator [1].

Irregular menstruations with anovulatory cycles or amenorrhea have negative effects on bone formation and total bone mass. They lead to a lack of estradiol and are associated with inadequate and unbalanced nu-trition. This results in severe impairment of bone for-mation and a net loss of bone mass[23].

Hormones play an integral part on bone mass. Evi-dence suggests that the hypothalmic-pituitary-thyroid axis (HPT) and the hypothalmic-pituitary-ovarian (HPO) axis are physiologically related and act together in certain conditions. Specific thyroid hormone re-ceptors at the ovarian level may regulate reproductive function, along with estrogens at the higher levels of the HPT axis. Hyperthyroidism and hyperparathy-roidism are also associated with bone loss. Hyper- and hypo- thyroidism can cause menstrual complications. Hyperthyroidism leads to oligomenorrhea, anovulato-ry cycles and bleeding, while hypothyroidism is mainly characterized by polymenorrhea, in mature women [24,25]. The hypothalmic-pituitary-gonadal axis is crucial for the function of the gonads. Other factors, such as catecholamines exert non-endocrine regulatory influ-ences within the gonads. Catecholamimes can alter blood flow, steroidogenesis and gene expression, de-pending on the target cells[21,26] . Another hormone of major concern that is associated with exercise and which indirectly affects bone loss is oxytocin (Oxt). Oxt acts in the lumbar spinal cord and accentuates the reflex pressor (mean arterial pressure - MAP) and heart rate (HR) responses to static hindlimb contraction. Endogenous Oxt modulates the exercise pres-sor reflex by its action on Oxt receptors in the lumbar spinal cord, which accentuates sensory nerve transmis-sion from skeletal muscle [27].

Etiology

Osteoporosis is multifactorial. Intrinsic risk factors in-clude ethnicity (Caucasian or Asian), a positive family history, gender, and certain medical disorders, includ-ing thyrotoxicosis, Type I diabetes, rheumatoid arthri-tis, and Cushing's syndrome. Stehman-Breen et.al., re-ported that black patients with end-stage renal disease (ESRD) have a greater BMD and are at a decreased risk for osteopenia compared with whites, independent of renal osteodystrophy. Physicians should consider os-teoporosis and the impact of race on BMD when con-sidering bone disease among patients with ESRD [28]. Late menarche, amenorrhea and early menopause are other intrinsic factors for osteoporosis [29]. Extrinsic or modifiable risk factors include estrogen and calcium deficiencies, a sedentary lifestyle, smoking, excessive alcohol intake [30], amount of salt intake [31] and cer-tain medical conditions [30].

Menstrual disturbances have been known to affect female athletes who are vegetarian. The basis for de-termining if vegetarianism will have an impact on fe-male's energy imbalances associated with body-weight disturbances or exercise, psychosocial and cognitive factors, and dietary components must be evaluated. Some studies suggest that clinical menstrual problems may be more common in vegetarians. A prospec-tive study found that subclinical problems were less common in weight-stable, healthy vegetarian women. However, the sample does not represent all vegetar-ian women, and so the results cannot be generalized [32]. In one study investigating the pathogenesis of age-related osteoporosis in Chinese women with low calcium intakes, reported that age-related osteoporosis might be linked with inefficient intestinal calcium ab-sorption and bone remodeling. The Chinese women were found to have potent intestinal calcium absorp-tion [33]. Cigarette smoking is linked to a variety of hormone-related disorders, both benign and malignant, due to its antiestrogenic effect [34]. Osteopenia can cause osteoporosis. A common cause of osteopenia is glucocorticoid administration[22,35]. It is known incidence of atraumatic fractures in patients receiving long term glucocorticoid therapy and is reported to be around 30%-50% [36-38]. Glucocorticoids decrease osteoblast activity and intestinal calcium absorption and may have effects on calcium regulatory hormones [39,40].

Anticonvulsants reduce bone density through their ef-fects on vitamin D metabolism [41-43] and by directly affecting bone turnover [44-46]. Contrarily, Vitamin D is not a factor for premenopausal women who receive incidental sun exposure or consume fortified foods, but supplementation can be considered for others[47]. Other agents associated with causing osteoporosis are corticosteroids, thyroid hormone, antacids containing aluminum, heparin, cancer chemotherapy, tetracycline, isoniazid, and immunosuppressive agents. However, in contrast to osteopenia associated with estrogen defi-ciency, cortical bone mass is lost in the latter[10]. A hormonal imbalance in athletes leads to osteoporosis and increased incidence of fracture. Athletes have de-creased levels of sex hormones, which can cause phys-iological changes that can lead to bone loss [45,48].

Female athletes are at an increased risk for certain sports-related injuries involving the knee. The differ-ences in sports undertaken and the gender anatomy and structure can contribute to this risk. Baseline level of conditioning, lower extremity alignment, physiolog-ical laxity, pelvis width, tibial rotation and foot align-ment are all gender differences. Sports like gymnastics and cheerleading create a noncontact environment, but can cause severe knee injuries. In quick stop or cut sports, female athletes have an increased incidence of anterior cruciate ligament injury through noncontact mechanisms [47].

Female Athlete Triad

In 1992, the American College of Sports Medicine coined the term the female athlete triad, which de-scribes a serious, yet preventable syndrome, compris-ing 3 interrelated components: (a) disordered eating, (b) amenorrhea, and (c) osteoporosis [49]. Young women are under great pressure to achieve or main-tain unrealistically low body weight in a short period of time. This is one of the underlying components of the female athlete triad. Adolescents and women training in sports, who emphasize on a low body weight, are at greater risk [50]. The symptoms of the triad and the severity of the disorder should be recognized by the physician [2,51-54].

Amenorrhea And Osteoporosis

Amenorrhea is abnormal absence or suppression of menstruation. It is a common problem for female athletes and may contribute to stress fractures and osteoporosis [55,56]. Amenorrhea decreases bone density at an age when bone formation should still be occurring. Failure to attain sufficient bone density during

the premenopausal years can result in insuffi-cient skeletal mass after menopause when the rate of bone loss exceeds that of bone formation. Primary and secondary amenorrheas are two types of amenor-rhea. Primary amenorrhea describes a state in which a female has not experienced menarche by either 16.5 years of age or within 2 years after the development of secondary sexual characteristics. Secondary amenor-rhea is associated with the absence of menstruation for greater than 6 months in a woman with previously normal cycles [33].

There are many causes of amenorrhea. The most common is physiologic amenorrhea due to pregnan-cy or nursing. Causes of primary amenorrhea include anatomic abnormalities, gonadal failure, and condi-tions of the hypothalmic-pituitary-ovarian (HPO) axis. Three important causes of secondary amenorrhea are:

(1) Rigorous physical exercise, (2) anorexia nervosa, and (3) use of medroxyprogesterone acetate injection (Depo-Provera) [33]. A direct correlation between ex-ercise and menstrual disorders has been established. However, the mechanism by which exercise disrupts reproductive function remains unknown. Studies have reported that low energy availability rather than inad-equate body fat or exercise stress most likely represents the mechanism by which exercise has a negative effect on the HPO axis in female athletes [57]. Pre-pubertal exercise may contribute to the prevention of osteo-porosis by increasing BMD; exercise during puberty is correlated with primary amenorrhea and low peak BMD, and exercise after puberty is linked with second-ary amenorrhea and bone loss [58]. Evidence suggests that exercise-related menstrual irregularities (ERMI) are produced by a disturbance of the hypothalmic gonadotrophin-releasing hormone oscillator. This disturbance may either be caused by either an insufficient estrogen or progesterone feedback or by an imbalance of opioid peptide and catecholamine activities medi-ated by GABA, corticotrophin-releasing hormone and insulin-like growth factor-1[59]. Amenorrheic female athletes are reported to have an increase in potential for lipid peroxidation after exercise. This might have a potential association with low levels of E2 [60].

Hypothalmic amenorrhea (HA) is a type of secondary amenorrhea which is frequently observed in women athletes and female anorexics [61]. Body weight, body composition, eating attitudes, and exercise are modula-tors of the gonadotrop axis [62]. It is a consequence of low dietary intake as observed in two conditions, anorexia nervosa, and intensive exercise. Prolonged mild dieting characterized by a fat restriction could interfere with gonadotropin secretion. However, the gonadotropin deficiency is partial and may be revers-ible after improving diet and body composition [63]. HA is caused by many factors, such as an interruption in the release of GnRH, which indirectly causes a de-crease in the levels of estrogen and progesterone [64]. However, the mechanism by which stress alters GnRH secretion is not thoroughly understood [65]. Women affected by functional hypothalmic secondary amenorrhea do not respond to stress as usual [66,67]. In diabetic female athletes, diabetes has also been linked to secondary hypogonadotrophic amenorrhea. In amenorrheic women with insulin-dependent diabetes, a derangement in HPO axis has been proposed. In a study with GnRH, corticotrophin releasing hormone, metoclopramide, and thyroid releasing hormone tests were performed in 15 diabetic women, 8 amenorrhe-ic (AD) and 7 eumenorrheic (ED). The AD women showed lower plasma levels of LH, FSH, prolactin, oestradiol, androstenedione and 17-hydroxyprogesterone than the ED women. The AD women also had a lower prolactin response TRH and metoclopramide, and lower ACTh and cortisol responses to CRH, rel-ative to the ED women [68]. This type of diabetes may involve mild chronic hypercortisolism that may affect metabolic control. Stress-induced activation of the hypothalmic-pituitary-adrenal axis would increase hypothalmic secretion of CRH, which in turn would inhibit GnRH secretion by increasing dopaminergic tonus, which consequently lead to hypogonadotrophic amenorrhea[68].

Menstrual disturbances in women can have critical effects on the skeletal system. At the lumbar spine, menstrual disturbances are associated with premature bone loss or failure to reach peak bone mass, while appendicular sites is less affected. Trabecular bone is observed to be more sensitive to hormonal stimuli and less responsive to mechanical loading than corti-cal bone [69]. There have been studies, which show menstrual dysfunction was related to muskuloskeletal injuries in women distance runners [70] and ballet dancers, with a prevalence of up to 66%[71]. In addi-tion, half of the athletes were classified as being at risk for developing eating disorders [71]. However, studies show that the BMD of former amenorrheic athletes normalizes following several years of normal menses or use of oral contraceptives, if early intervention is taken [72].

Leptin

Leptin, the product of the obesity gene, is produced in several organs additional to white adipose tissue, in-cluding brown fat, and the placenta and fetal tissues. It is a 16-kDa adipocyte-secreted protein whose serum levels reflects the amount of energy stores and is in-fluenced by short-term energy imbalance as well as cy-tokines and hormones. It binds to specific receptors, altering the expression of hypothalmic neuropeptides that regulate neuroendocrine function as well as energy intake and expenditure. Evidence suggests that leptin may send information to the brain for LHRH secre-tion and activation of the hypothalmic-pituitary-go-nadal axis [73]. Leptin may stimulate release of GnRH from the hypothalamus and of gonadotrophins from the pituitary [74]. However, effects of mild dieting on bone mineral density likely suggests an estrogen-inde-pendent mechanism for bone loss, and involves some of the metabolic hormones altered through amenor-rhea. These hormones play a vital role in modulating bone turnover and bone mineral density [75].

Leptin modulates the secretion of LH, but not the se-cretion of GnRH-LH [69]. Initiation of puberty in animals and humans has been correlated with rising leptin levels. Normal leptin levels are integral to the maintenance of menstrual cycles and normal repro-ductive function. Circadian and ultradian variations of leptin levels are associated with minute-to-minute vari-ations of LH and estradiol in normal women [73], the functions involving: inhibiting food intake, stimulation of energy expenditure, and signaling within the repro-ductive system [76,77].

Women who were anorexic or who participated in strenuous exercise experienced a decrease in leptin levels in response to starvation. Consequently, this re-sulted in a decrease in estradiol levels and amenorrhea [75]. Leptin levels in females with anorexia nervosa are low and are related to BMI. However, leptin levels in particular female athletes were even more decreased through the amount of low fat storage [78]. Further studies have assessed the relationship of decreased leptin levels with other hormonal abnormalities in an-orexia nervosa and reported that leptin is a necessary, but not essential factor, for the resumption of menses in anorexia nervosa patients [79].

Diagnosis

Osteoporosis in female athletes is usually diagnosed in-cidentally when examining x-rays for an initial fracture.

On X-rays, radiolucency may indicate osteoporosis [10,80] of the appendicular skeleton, portraying corti-cal thinning and the loss of trabecular bone, especially in the femoral neck. In order for a standard X-ray to detect osteoporosis, 25% to 30% of the bone mineral content must be already been lost[10,81].

Blood and urine content can also be measured for de-tecting osteoporosis. Bone resorption markers that are released into the bloodstream are excreted into the urine. Markers for bone formation are measured in the serum. Examples include hydroxyproline, calcium, phosphorous, and cyclic AMP. BMD can be measured through invasive or noninvasive methods. Invasive methods include a bone biopsy taken from the iliac crest [82,83] and a histometry which determines the degree of bone mineralization, the quantity and struc-ture of the trabecular bone, the number of active bone cells, and the rates of bone formation and resorption. Double tetracycline-labeled bone biopsies are helpful in evaluating patients with suspected osteomalacia or renal osteodystrophy before interventions, such as sur-gical parathyroidectomy [84]. Noninvasive methods, such as plain radiographs [10,81-83,85], radiogram-metry [81,83], single photon absorptiometry [81,82], dual photon absorptiometry [81,83,85-87], computed tomography[83,85], quantitative digital radiography [88], nuclear scanning of total body calcium and reten-tion of [87] Tc-labeled pyrophosphate are used. An-other very important test is height [89]. It should be measured accurately by a stadiometer. If the difference between how tall the patient perceives to be and the measured amount is greater than 1.5-inches, there is a strong probability that the patient has had an asympto-matic vertebral compression fracture. Vertebral com-pression fractures are predictive and diagnostic of fu-ture fractures [84].

Osteoporosis in women athletes can only be detected incidentally[90]. However, there are certain signs and symptoms that physicians should be aware of. More athletes competing in leanness sports were classified as being at risk of the female athlete triad compared with athletes competing in non-leanness sports [56,91]. Likewise, the Russell's sign should be observed. This sign consists of skin lesions, consisting of abra-sions, small lacerations, and callosities on the dorsum of the hand overlying the metacarpophalangeal and interphalangeal joints. These are caused by repeated contact of the incisors with the hand while inducing vomiting. Recognizing this sign can have profound ef-fects on the patient's musculoskeletal system and gen-eral health [53,92].

Treatment

Athletes with amenorrhea and who develop fractures easily should be screened for osteoporosis. Treatments include calcium supplementation, salmon calcitonin, estrogen, vitamin D, anabolic steroids, diphospho-nates, fluoride, and coherence therapy. The National Institutes of Health Consensus conference recom-mended 1.5-g of elemental calcium with vitamin D (400-IU per day) for all postmenopausal women [93]. Women older than 65 should take 1.5-g of elemental calcium with 800-g of vitamin D daily[94,95]. The FDA has approved a nasal spray form of salmon calci-tonin. The dose is 200-IU per day in one nostril [96]. Calcitonin has been reported to increase bone mass by 5%-20% [97,98]. It should be used for women who are 5 years postmenopausal, have low bone density and are unwilling to take estrogen. Estrogen replace-ment therapy reduces the rate of bone turnover and inhibits bone resorption [99,100]. When prescribed judiciously, many female athletes will benefit from the use of estrogen[101]. Raloxifene was approved by the FDA as a selective estrogen receptor modulator. Ra-loxifene acts as an estrogen agonist in some tissues and an estrogen antagonist in others. 2 years of treatment with raloxifene, at a dose of 60-mg per day, has shown to increase BMD in postmenopausal women. Clinical studies show that estrogen and estrogen-androgen re-placement therapies both prevent the development of osteoporosis, as determined by bone mineral density determinations and bone marker analyses. By adding androgen to hormone replacement therapy, bone loss may be prevented and bone formation may be stimu-lated [102,103]. Biphosphonates can also be used. Bi-phosphonates are pyrophophate analogues, in which a carbon has replaced the oxygen in P-O-P, resulting in a P-C-P structure [104]. These are powerful inhibi-tors of bone resorption. Biphosphonates reduce the absorption activity of osteoclasts or enhance the os-teoforming activity of osteoblasts. Biphosphonates create a positive balance of the remodeling cycle, and increase the density of bone mass, lessening the inci-dences of bone fractures [105]. Alendronate is the only biphosphonate that is approved by the FDA, having the ability to reduce the incidence of fractures [93]. 5-mg of alendronate should be taken to prevent osteo-porosis and 10-mg should be taken to treat osteoporo-sis [95]. Alendronate at 10-mg per day increased BMD at the spine by 6%-8% and at the hip by 4%-6% over a 3 year period, according to studies of postmenopausal women. Stimulators of bone formation include sodi-um fluoride, calcitrol, PTH, growth hormone, growth factors, prostaglandin, strontium salts and anabolic steroids [106]. PTH prevents bone loss from the prox-imal femur and total body and increases lumbar spinal BMD in young women with GnRH induced estrogen deficiency [107].

For treatment of secondary forms of osteoporosis, such as steroid-induced osteoporosis, alendronate has been approved in the US [84] and etidronate has been approved in the UK and Canada [106]. Exercise is an-other effective treatment and several studies with post-menopausal women show modest increases in bone mineral in response to training. It has been suggested that training can be used to improve effects on BMD in postmenopausal females. Bone geometry and mass dis-tribution can be changed as a result of training or hor-monal replacement therapy, thereby improving bone strength and reducing fracture risk. Training continues to stimulate increases in bone diameter throughout the lifespan. These types of exercise stimulate increases in bone diameter, diminish the risk of fractures by me-chanically counteracting the thinning of bones, and increases bone porosity [108,109]. However, there is no agreement on the quantity, frequency and type of exercise[110,111]. Weight-bearing exercise is recom-mended three times per week for one-half hour each [109,112]. It should be noted that the patient must commit to the exercise, in order to sustain BMD al-ready gained[96].

Discussion

It is important that women participate in sports and develop skills that promote lifelong athletic participa-tion. However, when one engages in strenuous exer-cise, serious complications can arise. Disorders, such as amenorrhea, eating disorders and osteoporosis, are common complications that can occur in female athletes [113]. Proper screening, diagnosis and treatment should be accommodated to promote a healthy life-style. More research is needed in the area of female athletes and osteoporosis. Howev-

er, along with this research, physicians, coaches, trainers, female athletes, and parents need to be educated about the associa-tion of athletes and the female athlete triad, with os-teoporosis as a crucial component. Detailed history and physical examination provide a great opportunity to detect triad disorders and educate female athletes on the importance of a healthy nutrition, normal men-strual function, and exercise associated with osteopo-rosis [114]. Delay or failure to recognize and manage these patients may result in the emergence of athletic triad with potential seri-ous consequences of increased stress fractures, scoliosis, and thin body mass.

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