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Body composition and reproductive function exert unique influences on indices of bone health in exercising women

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ABSTRACT

Reproductive function, metabolic hormones, and lean mass have been observed to influence bone metabolism and bone mass. It is unclear, however, if reproductive, metabolic and body composition factors play unique roles in the clinical measures of areal bone mineral density (aBMD) and bone geometry in exercising women. This study compares lumbar spine bone mineral apparent density (BMAD) and estimates of femoral neck cross-sectional moment of inertia (CSMI) and cross-sectional area (CSA) between exercising ovulatory (Ov) and amenorrheic (Amen) women. It also explores the respective roles of reproductive function, metabolic status, and body composition on aBMD, lumbar spine BMAD and femoral neck CSMI and CSA, which are surrogate measures of bone strength. Among exercising women aged 18–30 years, body composition, aBMD, and estimates of femoral neck CSMI and CSA were assessed by dual-energy x-ray absorptiometry. Lumbar spine BMAD was calculated from bone mineral content and area. Estrone-1-glucuronide (E1G) and pregnanediol glucuronide were measured in daily urine samples collected for one cycle or monitoring period. Fasting blood samples were collected for measurement of leptin and total triiodothyronine. Ov ($n = 37$) and Amen ($n = 45$) women aged 22.3 ± 0.5 years did not differ in body mass, body mass index, and lean mass; however, Ov women had significantly higher percent body fat than Amen women. Lumbar spine aBMD and BMAD were significantly lower in Amen women compared to Ov women ($p < 0.001$); however, femoral neck CSA and CSMI were not different between groups. E1G cycle mean and age of menarche were the strongest predictors of lumbar spine aBMD and BMAD, together explaining 25.5% and 22.7% of the variance, respectively. Lean mass was the strongest predictor of total hip and femoral neck aBMD as well as femoral neck CSMI and CSA, explaining 8.5–34.8% of the variance. Upon consideration of several potential osteogenic stimuli, reproductive function appears to play a key role in bone mass at a site composed of primarily trabecular bone. However, lean mass is one of the most influential predictors of bone mass and bone geometry at weight-bearing sites, such as the hip.

Introduction

Amenorrheic exercising women typically present with low bone mineral density (BMD) when compared to their ovulating counterparts [1–3]. The poor bone health observed among amenorrheic exercising women is due to the uncoupling of bone formation and resorption that occurs in an environment of low energy availability and suppressed estrogen activity [4,5]. Estrogen has known osteogenic benefits, serving as a key inhibitor of osteoclast action [6]. Amenorrheic women present with suppressed concentrations of estrogen which may contribute to elevated resorption and, ultimately, poor bone health as evidenced by low BMD and impaired bone geometry and microarchitecture [4,5,7–9]. Likewise, the metabolic environment characteristic of exercising women with functional hypothalamic amenorrhea (FHA), i.e. suppressed insulin-like growth factor-1 (IGF-1), leptin, and total triiodothyronine (TT3), may also contribute to compromised bone health due to its potentially detrimental impact on bone formation [4,5].

In addition to suppressed reproductive hormone concentrations and altered metabolic profile, another characteristic that may differentiate amenorrheic and ovulatory women is fat mass. Exercising women with FHA typically have a lower fat mass or percent body fat than ovulatory exercising women, serving as another possible contributing factor to poor bone health due to the potentially osteogenic

Abbreviations: aBMD, areal bone mineral density; Amen, amenorrheic exercising women; AUC, area under the curve; BMAD, bone mineral apparent density; BMI, body mass index; CSA, cross-sectional area; CSMI, cross-sectional moment of inertia; DXA, dual-energy x-ray absorptiometry; EAMD, exercise-associated menstrual disturbances; E1G, estrone-1-glucuronide; FHA, functional hypothalamic amenorrhea; HSA, hip strength analysis; IGF-1, insulin-like growth-factor-1; LH, luteinizing hormone; Ov, ovulatory exercising women; PdG, pregnanediol glucuronide; pQCT, peripheral quantitative computed tomography; TT3, total triiodothyronine; VO_{2max}, maximal aerobic capacity.

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effects of the adipocyte-derived hormone leptin on BMD [10–12]. Furthermore, an energy deficit can cause a decrease in circulating concentrations of leptin prior to changes in fat mass, indicating that a harmful environment for bone health may be present prior to changes in body weight and may be exacerbated by subsequent changes in body composition that occur as energy deficiency is prolonged [13]. Another large component of body composition, lean mass, has been repeatedly demonstrated to exert strong osteogenic effects on bone mass [14,15]; however, less is known about the influence of body fat on bone health. Therefore, although reproductive function, metabolic hormones and body composition, particularly lean mass, have been observed to be important for bone health when each component is viewed individually, it is currently not clear whether reproductive function, the metabolic milieu, or body composition, to include both lean body mass and fat mass, is a stronger predictor of bone health among exercising women.

When assessing bone health, BMD is obtained from dual-energy x-ray absorptiometry (DXA), a technique that is only capable of measuring areal BMD (aBMD) rather than true volumetric BMD [16]. Areal BMD tends to underestimate true BMD in small, thin individuals and overestimate true BMD in taller, larger individuals. Therefore, an algorithm that corrects for bone size has been developed to estimate volumetric BMD (bone mineral apparent density or BMAD) at the lumbar spine [16], a site that is prone to low BMD among amenorrheic women and osteoporotic fractures in aged women [2,3]. Investigators have previously reported low lumbar spine BMAD among amenorrheic adolescent athletes compared to eumenorrheic adolescent athletes and non-athletic girls [3,8]. Likewise, retired elite gymnasts with a history of amenorrhea were also reported to have lower lumbar spine BMAD compared to retired gymnasts without a history of amenorrhea [9]. Among both adolescent girls and adult women with anorexia nervosa, a severe model of energy deficiency, Karlsson et al. [17] and Misra et al. [18] reported lower lumbar spine BMAD compared to age-matched controls. Therefore, it appears that both an estrogen and energy deficiency contribute to lower lumbar spine BMAD among adolescent girls and women; however, lumbar spine BMAD has not been assessed, to date, in exercising women with a current presentation of FHA.

In addition, DXA is unable to measure bone geometry, an important component of bone strength. However, three-dimensional techniques such as quantitative computed tomography (QCT) and peripheral QCT (pQCT) which can assess bone geometry involve a higher radiation dose than DXA and may not be as readily available as DXA. Therefore, due to the widespread clinical use of DXA and the importance of bone geometry in determining bone strength and fracture risk, a method of estimating geometric properties of the femoral neck using DXA, termed hip strength analysis (HSA) has been developed [19,20]. HSA provides an estimate of femoral neck strength via measurements of cross-sectional area (CSA) and cross-sectional moment of inertia (CSMI) [19,21], and, in essence, has enhanced traditional DXA measurements by allowing for an estimate of not only bone mass but also bone geometry, two key components of bone strength. Investigations that go beyond DXA-derived aBMD may not only provide a better estimate of bone strength and fracture risk in amenorrheic women but may also help to identify the determinant factors that affect skeletal fragility in this population.

The roles of body composition, metabolic status, and reproductive function in the parameters of bone health derived from DXA such as aBMD, lumbar spine BMAD, and femoral neck CSA and CSMI are currently not well-understood. Therefore, the purpose of this study is twofold. This study seeks 1) to determine if amenorrheic and ovulatory exercising women differ with regard to DXA-derived estimates of volumetric density of the lumbar spine (lumbar spine BMAD) and femoral neck strength (femoral neck CSMI and CSA) and 2) to explore the respective roles of reproductive function, metabolic status, and body composition, i.e. fat mass and lean mass, in aBMD, lumbar spine BMAD and femoral neck CSMI and CSA. It is hypothesized that 1) amenorrheic exercising women will demonstrate lower lumbar spine BMAD, and lower femoral neck CSMI and CSA compared to ovulatory exercising women, and 2) estrogen and progesterone exposure, age of menarche, leptin and TT3, and lean mass and fat mass will be significant predictors of bone health parameters (aBMD, lumbar spine BMAD, femoral neck CSA and CSMI) among exercising women but will exert differing influences depending on the bone site.

Methods

Study design

This study is a cross-sectional analysis comparing eumenorrheic exercising women with ovulatory menstrual cycles (Ov, $n = 37$) and exercising women with amenorrhea (Amen, $n = 45$). Women were considered exercising if they participated in at least 2 hours of purposeful physical activity per week. To confirm menstrual status, each woman collected daily urine samples for at least one menstrual cycle if eumenorrheic or one 28-day monitoring period if amenorrheic, and urinary concentrations of reproductive hormones were subsequently assessed. The current study includes data from a cross-sectional study that assessed the impact of menstrual function on cardiovascular and bone health in exercising women and baseline data from a randomized controlled trial designed to determine the effects of a 12-month intervention of increased caloric intake on indices of bone health and menstrual status in premenopausal women who suffer from severe exercise-associated menstrual disturbances (EAMD).

Participants

Participants were recruited by newspaper advertisements, fliers, and classroom announcements targeting physically active women. Inclusion criteria for this study were: 1) age 18–30 years; 2) weight stable (± 2 kg) for at least 3 months; 3) good health and no history of any serious medical conditions; 4) no chronic illness, including hyperprolactinemia and thyroid disease; 5) no current clinical diagnosis of an eating or psychiatric disorder; 6) non-smoking; 7) not taking any form of hormonal therapy for at least 6 months; 8) ≥ 2 h/week aerobic exercise; 9) no history of a clinical diagnosis of polycystic ovarian syndrome or evidence of hyperandrogenism; 10) eumenorrheic, ovulatory cycles of 26–35 days if regularly menstruating; 11) no menses for at least 90 days or ≤ 3 cycles in the past 6 months if amenorrheic. It has been reported that reproductive function of women who are more gynecologically mature may be less susceptible to perturbation than that of younger women [22]; therefore, to maintain an age-matched sample, the two 30-year old Ov women who were recruited were excluded from analysis.

Study procedures

During an initial visit, participants were informed of the purpose, procedures, and potential risks of participation in the study before signing an informed consent approved by either the Human Ethics Board at the University of Toronto or Biomedical Institutional Review Board at the Pennsylvania State University. Once consent was obtained, height and weight were measured, and participants completed questionnaires to assess demographics, medical history, exercise history, menstrual history, eating behaviors [23,24], and bone health.

Classification of baseline menstrual status

Upon study entry, classification of menstrual status was based on self-reported menstrual histories and was confirmed by urinary estrone-1-glucuronide (E1G), pregnanediol glucuronide (PdG), and