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BONE MINERAL DENSITY AND HORMONAL STATUS IN ADOLESCENT ATHLETIC GIRLS

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ABSTRACT

The aim of this study was to determine the relationships of bone mineral density (BMD) and content (BMC) with selected fasting hormones in adolescents with different exercise training patterns. The participants were female athletes of weight-loaded (n=23) and weight-supported (n=24) sports, and 33 non-athletic girls aged 13–15-years. BMD (g/cm^2) and BMC (g) at the femoral neck (FN) and lumbar spine (LS) were measured. Venous blood samples were drawn to determine the concentration of insulin-like growth factor-1 (IGF-1), IGF binding protein-3 (IGFBP-3), estradiol, visfatin, adiponectin, leptin, insulin, and glucose. After adjusting for age, height, and body mass, the relationships of BMD variables with IGF-1, IGF-1/IGFBP-3 molar ratio, estradiol, and leptin levels remained significant only in the weight-loaded sport group ($r=0.41–0.60$; $p<0.05$). Adiponectin was inversely correlated to FN and LS BMD and BMC ($r=–0.47–0.62$; $p<0.05$) in weight-supported sport group only, but after adjustments for age, height, and body mass, these associations disappeared. In this study, concentrations of visfatin, a fairly new adipocytokine, were not related to bone parameters in adolescent girls with different training patterns.

Keywords: *bone health; insulin-like growth factor-1; estradiol; adipocytokines; adolescent female athletes*

INTRODUCTION

Bone is a unique, metabolically active tissue that undergoes a continuous remodelling throughout its life cycle. A great number of factors influence the accumulation of bone mineral in humans. Some are endogenic, such as heredity, ethnicity, gender, or endocrine status; the others – exogenic, such as nutrition or physical activity [12, 23]. Bone mineral is substantially accrued throughout childhood and puberty through the concerted influences of growth and systemic hormones [15]. In girls, bone development may be especially promoted by the increase of estrogen and free, biologically active insulin-like growth factor-1 (IGF-1) levels which occurs at the time of menarche and peak bone mineral accrual velocity, corresponding to ages of 11.5–13.5 years [15]. Evidence exists that several adipocytokines may also have a positive influence on bone mineral density (BMD) of the growing skeleton [8]. Visfatin, adiponectin, and leptin, the cytokine-like hormones, are suggested to carry signals from adipose tissue to bone and contribute to the relationship between fat mass and BMD [10, 11, 14, 27].

It is well known that mechanical loading activity on bone is vitally important for skeletal strength and development. Maximizing BMD and bone mineral content (BMC) during the growing years by adopting weight-bearing physical activity in childhood and adolescence may be one of the most effective osteoporosis prevention strategies [7]. Adolescents engaged in weight-bearing sports (such as gymnastics) appear to achieve significantly greater regional and whole-body gains in bone mineral than adolescents involved in weight-supported activities (such as swimming) [9]. The nature of the sport may affect bone mineralization in adolescent athletes due to a relative state of energy deficiency and changes in body fat mass [17]. Evidence suggest that bone health can be compromised if IGF-1 and estrogen levels are low, particularly in those young female athletes who participate in competitive sports where leanness may be emphasised or aesthetically pleasing (i.e. gymnasts or swimmers) [1, 29]. Nevertheless, Courteix et al. [5] suggested that physical activity has beneficial effects on bone that may counterbalance such negative factors of bone health such as low fat mass and insufficient blood leptin levels in adolescent females.

The possible synergism between advancing pubertal status and loading induced bone gain suggests that a "window of opportunity" for bone response may exist in early puberty [15]. However, little information is available concerning the relationships between bone parameters and fasting hormones, especially different adipocytokines, in adolescent female athletes. The aim of this study was to determine the relationships of BMD and BMC with IGF-1, IGF binding protein-3 (IGFBP-3), estradiol, and selected adipocytokines (visfatin, adiponectin, and leptin) in adolescent girls with different training patterns.

MATERIALS AND METHODS

Subjects

In total, 80 healthy 13–15-year-old girls from different schools and sport clubs in Estonia (Tallinn, Tartu, Pärnu) took part in this cross-sectional study. Before entering the study, volunteers completed simple medical and physical activity questionnaires to provide information such as the onset of the training and weekly hours of participating in sports. All participants were free from past or present diseases known to affect skeletal metabolism. None of the girls used birth control or medications known to affect bone. Girls were also asked not to change their eating habits [13]. The participants comprised three groups: athletes of weight-loaded (rhythmic gymnastics; n=23) and weight-supported (swimming; n=24) sports, and 33 nonathletic healthy girls (untrained controls). The athletic girls must have participated in their selected sports for at least for the last two years (Table 1). Control group girls only took part in compulsory physical education classes at school (i.e. 45 min twice per week). Each girl and her parent (or legal guardian) received a full written description of the nature of the study and signed an informed consent form before participating. The study was approved by the Medical Ethics Committee of the University of Tartu (Estonia).

Measures

Body height and sitting height were measured to the nearest 0.1 cm using the Martin's metal anthropometer. Body mass was measured to the nearest 0.05 kg using medical scales (A&D Instruments Ltd, Abingdon, UK). The girls were dressed in light clothing and wearing no shoes. Body height and body mass data were used to calculate body mass index (BMI) (kg/m^2). The determination of years from the attainment of peak height velocity (PHV) – an indicator of somatic maturity, reflecting the maximum velocity in statural growth during adolescence – was used to assess physical maturity of the participants [2]. Predicted age at PHV (APHV) and biological maturity age (how many years a girl was from APHV) of the participants was estimated using chronological age, body height, sitting height, and body mass data (the predictive equation may be accessed at http://taurus.usask.ca/growthutility/ using one of the Childhood Growth Utility Programs developed by members of the Saskatchewan Childhood Growth and Development Research Group based in the College of Kinesiology, at the University of Saskatchewan, Saskatoon, Saskatchewan, Canada) [2]. The girls were also asked if they had experienced menarche. The data on the age at menarche and the duration of a single menstrual cycle of the girls was obtained using a simple questionnaire.

BMD (g/cm^2) and BMC (g) at femoral neck (FN) and lumbar spine (L2-L4) (LS) were measured by dual-energy X-ray absorptiometry (DXA) using the DPX-IQ densitometer (Lunar Corporation, Madison, WI, USA) equipped with proprietary software, version 3.6. DXA measurements and results were evaluated by the same examiner. Coefficients of variations (CVs) for BMD and BMC measurements in female adolescents were less than 2%.

Venous blood samples to determine the concentration of IGF-1, IGFBP-3, estradiol, visfatin, adiponectin, leptin, insulin, and glucose were drawn between 07:30 and 08:30 a.m. after an overnight fasting. For those girls who had regular menstruation, the fasting blood samples were drawn in the early follicular phase of the menstrual cycle, i.e. days 5–7 after menstrual bleeding started [13]. The levels of IGF-1, IGFBP-3, estradiol and insulin concentrations were analyzed on Immulite 2000 radioimmunoassay (DPC, Los Angeles, CA, USA). The intra- and inter-assay CVs for IGF-1, IGFBP-3, and estradiol were <7%. The intra- and inter-assay CVs for insulin were <5% and <12%, respectively, at an insulin concentration of 6.6 μIU/mL. The levels of visfatin and adiponectin concentrations were analyzed using ELISA kits (AdipoGen and Mediagnost, Aspenhaustr, Germany). The intra- and inter-assay CVs for visfatin were <10% and <8%, and for adiponectin – <5% and <6%, respectively. For leptin concentration an ELISA sandwich (DRG Instruments GmbH, Marburg, Germany) analysis was used. The intra- and inter-assay CVs were <7% and <12%, respectively. Glucose concentration was measured with a commercial kit (Boehringer, Mannheim, Germany) that employed the hexokinase/glucose-6-phosphate dehydrogenase method. In addition, the IGF-1/IGFBP-3 molar ratio was calculated as it is suggested to be an indirect indicator of free IGF-1 [22]. The molar ratio was obtained as follows: IGF-1(ng/mL) x 0.130/IGFBP-3 (ng/mL) x 0.036 [18]. In addition, the insulin resistance index was calculated using homeostasis model assessment (HOMA): fasting insulin (μIU/mL) x fasting glucose (mmol/L)/22.5 [16]. The greater HOMA values indicate the greater level of insulin resistance.

Statistical analysis

Standard statistical methods were used to calculate means and standard deviations (±SD). Normality of parameters was controlled by one sample Kolmogorov-Smirnov test. Statistical comparisons between the groups were made using analysis of variance (ANOVA) and Tukey *post hoc* test. Pearson product moment correlation coefficients were computed to evaluate the relationships between bone mineral values and measured blood hormones. Partial correlation analysis was performed to assess these relationships while controlling for age, height, and body mass [26]. The effect of hormonal parameters to the BMD and BMC was analysed by stepwise multiple regression analysis.

Statistical significance was set at $p<0.05$ and all analyses were performed using SPSS 15.0 package for Windows (Chicago, IL, USA).

RESULTS

The physical characteristics of adolescent girls with different training patterns are presented in Table 1. Although athletes of weight-supported sport (i.e. swimmers) significantly differed from the athletes of weight-loaded sport (i.e. rhythmic gymnasts) and non-athletic girls in respect to the chronological age and predicted age at PHV, no significant differences were found in biological maturity between the studied groups. FN BMD was significantly greater of girls in weight-loaded sport group compared to weight-supported sport and non-athlete groups. No significant differences were found in BMC values between the studied groups. Girls of the weight-loaded sport group had trained significantly more years than those in the weight-supported sport group ($p<0.05$). No significant differences were found in blood biochemical parameters among the athlete and control groups (Table 2).

Table 1. Anthropometric, biological maturation, bone mineral values, and training history in adolescent girls with different training patterns (mean±SD)

	W-L athletes n=23	W-S athletes n=24	Non-athletes n=33
Age (yrs)	14.3 ±1.0	13.7 ±1.2§	14.2 ±1.1
Body height (cm)	163.8 ±6.7	164.2 ±6.8	163.3 ±6.5
Body mass (kg)	52.4 ±8.9	55.4 ±9.2	55.2 ±8.1
BMI (kg/m^2)	19.4 ±2.4	20.5 ±2.9	20.6 ±2.4
Predicted APHV (yrs)	12.4 ±0.5	12.0 ±0.4§	12.3 ±0.4
Biological maturity age (yrs)	1.9 ±0.9	1.7 ±1.0	1.9 ±0.9
Girls having menses [n (%)]	13 (56.5)	13 (54.2)	29 (87.9)
Menarcheal age (years)*	13.0 ±0.7	12.5 ±0.8	12.5 ±0.8
BMD femoral neck (g/cm^2)	1.13 ±0.15#	1.01 ±0.11	1.01 ±0.11
BMD lumbar spine (g/cm^2)	1.12 ±0.11	1.08 ±0.13	1.08 ±0.13
BMC femoral neck (g)	4.9 ±0.7	4.6 ±0.7	4.7 ±0.7
BMC lumbar spine (g)	44.5 ±8.2	41.6 ±9.9	41.4 ±7.9
Years of training	6.5 ±1.8	4.8 ±1.5†	–
Training duration (h/week)	9.6 ±4.9	9.4 ±3.2	–

Note: W–L – weight-loaded sport; W–S – weight-supported sport; BMI – body mass index; APHV – age at peak height velocity; BMD – bone mineral density; BMC – bone mineral content. *Of the girls that have experienced menarche. §Difference from weight-loaded sport athlete and non-athlete groups; $p<0.05$. #Difference from weight-supported sport athlete and non-athlete groups; $p<0.05$. †Difference from weight-loaded sport athletes; $p<0.05$.

Table 2. Blood biochemical parameters in adolescent girls with different training patterns (mean±SD)

	W-L athletes n=23	W-S athletes n=24	Non-athletes n=33
IGF-1 (μg/L)	443.2±104.9	463.7±138.6	419.2±144.9
IGFBP-3 (mg/L)	6.0±0.7	5.9±0.7	5.8±0.9
IGF-1/IGFBP-3 molar ratio	0.27±0.06	0.28±0.07	0.26±0.07
Estradiol (pmol/L)	67.7±35.2	108.0±91.4	103.1±134.5
Visfatin (ng/mL)	0.92±0.94	0.77±0.76	0.66±0.79
Adiponectin (μg/mL)	14.1±6.0	13.1±6.2	16.0±7.0
Leptin (ng/mL)	7.8±5.5	11.4±9.5	8.6±8.0
Insulin (μIU/mL)	5.6±3.2	5.0±3.5	6.0±3.5
Glucose (mmol/L)	4.9±0.3	4.9±0.4	4.8±0.3
HOMA	1.22±0.73	1.09±0.73	1.31±0.79

Note: W–L – weight-loaded sport; W–S – weight-supported sport; IGF – 1-insulin-like growth factor-1; IGFBP-3 – IGF-binding protein-3; HOMA – homeostasis model assessment

Significant correlations were found between IGF-1, IGF-1/IGFBP-3 molar ratio and both FN and LS BMD (r=0.39–0.59; p<0.05) in weight-loaded sport athletes and controls, but after adjusting for age, body height, and body mass, the relationships remained significant (r=0.46–0.52; p<0.05) only in the athlete group (Table 3). Similar trends were revealed regarding BMC values: the levels of IGF-1 and IGF-1/IGFBP-3 molar ratio were correlated with both FN and LS BMC (r=0.38–0.52; p<0.05) in non-athletes' group, but after adjustments were applied these relationships ceased to exist (data not shown). The relationships between IGF-1, IGF-1/IGFBP-3 molar ratio and FN BMC were significant (r=0.67–0.77; p<0.05) in the weight-loaded sport athlete group even after adjusting for age, body height, and body mass (data not shown). BMD values also correlated to estradiol levels (r=0.45–0.60; p<0.05), but in weight-loaded sport athlete group only. After adjusting for age, body height, and body mass, the associations remained significant (r=0.53–0.60; p<0.05). Visfatin concentrations were not correlated with FN nor LS BMD in any group (p>0.05). Adiponectin was found to be inversely related (p<0.05) to FN BMD (r=–0.48) and LS BMD (r=–0.60) in the weight-supported sport athlete group, however these relationships disappeared after controlling for age, body height, and body mass (Table 3). Leptin concentrations positively correlated with FN and LS BMD (r=0.43–0.52; p<0.05) in the weight-loaded sport athlete group only, even after adjustment for age, body height, and body mass (r=0.41–0.63; p<0.05). Similarly, no correlations were found between visfatin and BMC values in any

of the studied groups; the inverse correlation of adiponectin with FN and LS BMC (r=–0.47–0.62; p<0.05) in weight-supported group disappeared after controlling for age, body height, and body mass; and leptin concentrations positively correlated with FN BMC (r=0.56; p<0.01) in the weight-loaded sport athlete group only, even after adjustment for age, body height, and body mass (data not shown).

Table 3. Pearson correlation for BMD and hormonal variables in athlete and non-athlete groups. Partial correlation analysis (controlled for age, body height, and body mass) is presented in parenthesis

	W-L athletes n=23	W-S athletes N=24	Non-athletes n=33
BMD femoral neck (g/cm²)			
IGF-1 (μg/L)	0.59** (0.52*)	NS	0.54** (NS)
IGFBP-3 (mg/L)	NS	NS	NS
IGF-1/IGFBP-3 molar ratio	0.52* (0.46*)	NS	0.57** (NS)
Estradiol (pmol/L)	0.60** (0.60**)	NS	NS
Visfatin (ng/mL)	NS	NS	NS
Adiponectin (μg/mL)	NS	–0.48** (NS)	NS
Leptin (ng/mL)	0.43* (0.41*)	NS	NS
BMD lumbar spine (g/cm²)			
IGF-1 (μg/L)	0.56** (0.49*)	NS	0.39* (NS)
IGFBP-3 (mg/L)	0.44* (NS)	NS	NS
IGF-1/IGFBP-3 molar ratio	0.44* (NS)	NS	0.44* (NS)
Estradiol (pmol/L)	0.45* (0.53*)	NS	NS
Visfatin (ng/mL)	NS	NS	NS
Adiponectin (μg/mL)	NS	–0.60** (NS)	NS
Leptin (ng/mL)	0.52** (0.49*)	NS	NS

Note: W–L – weight-loaded sport; W–S – weight-supported sport; BMD – bone mineral density; IGF-1 – insulin-like growth factor-1; IGFBP-3 – IGF-binding protein-3. NS – not significant; Statistically significant, *p<0.05; Statistically significant, **p<0.01.

Stepwise multiple regression analysis indicated that IGF-1 and estradiol together explained 42.6% (R^2x100) of the total variance at FN BMD, and IGF-1 alone 35.4% (R^2x100) of the total variance at FN BMC in weight-loaded sport athlete group (data not shown).

DISCUSSION

The results of this study indicate that regular training in high-impact weight-bearing sport, such as rhythmic gymnastics, may positively contribute to the bone health of adolescent girls. In this group of athletes, the correlations of FN and LS BMD with IGF-1, estradiol and leptin, as well as FN BMD with IGF-1/IGFBP-3 molar ratio, and FN BMC with IGF-1, IGF-1/IGFBP-3 molar ratio and leptin remained significant even after adjusting for major confounders. Stepwise multiple regression analysis emphasised the association between IGF-1, estradiol and FN BMD as well as IGF-1 and FN BMC in this particular group. Similarly, Snow et al. [25] reported IGF-1/IGFBP-3 molar ratio to be the most robust predictor of FN BMD and suggested that IGF-1 may be a mediator of the muscle-bone relationship in young women with different exercise patterns.

Estradiol plays a significant role in bone formation. In pubertal females, estradiol inhibits bone resorption during growth and acts at higher concentrations to promote bone formation after menarche is reached [26]. Yilmaz et al. [28] found positive correlations between the levels of serum estradiol and BMD (LS and total body) in healthy non-athletic girls aged 10–15 years. It was observed that the increase in levels of serum estradiol at different pubertal stages in girls is accompanied by an increment in BMD values [28]. Our results suggest that regular weight-bearing physical activity during pubertal growth may positively affect bone mineralization, since estradiol and bone mineral values are interrelated significantly and independently from such major confounders as age, body height and body mass in the weight-loaded sport athlete group.

In female adolescents, Huang et al. [10] found that levels of adiponectin were negatively associated with total body BMD. The same authors reported positive associations between leptin and total body BMD [10]. Similar trends were observed in this study: FN and LS BMD were correlated inversely to adiponectin levels in the weight-supported sport athlete group; while FN and LS BMD had a positive relationship to leptin concentration levels in the weight-loaded sport athlete group. Evidence of the effects of visfatin on bone is scant: visfatin has been found to increase bone mineralization, promote glucose uptake, and downregulate osteocalcin secretion in human osteoblasts [27]. To date, only a few studies aimed to investigate the relationships of visfatin and bone mineral values in humans. Peng et al. [21] found visfatin to be related with hip BMD but not with LS or total body BMD in a population of Chinese men aged 20–80. In contrary, visfatin was not found to be an independent predictor of BMD in a population of post-menopausal Chinese women [30]. Recent investigation of the relationships of visfatin with bone density in middle-aged

patients with metabolic syndrome revealed plasma visfatin levels to be positively correlated to LS BMD in men, but not women [11]. Although the above mentioned studies involved older populations, to our knowledge the relationships of visfatin with bone mineral values were not studied in pediatrics to date. In our study, no significant correlations were observed between visfatin levels and bone mineral variables in adolescent girls with different training patterns. It may be suggested that visfatin, known to be associated with adiposity and contributing to the relationship between fat mass and bone mineral values, may not play a significant role in bone tissue development in relatively lean healthy adolescent females. In this study, in weight-loaded sport athlete group a trend for lower levels of estradiol and leptin concentration was observed and FN BMD was significantly higher than that of the weight-supported sport athlete and non-athlete groups. This is in consistence to the findings of other studies. Munoz et al. [19] found leptin concentrations to be lower and FN BMD higher in adolescent rhythmic gymnasts when compared to controls. Courteix et al. [5] reported leptin concentrations of rhythmic gymnast to be as low as those observed in anorectic subjects; nevertheless, the BMD and BMC values in gymnasts were greater than in controls, concluding that physical activity counterbalanced the negative effect that low fat mass and leptin deficiency has on bone. It seems that hypoestrogenism and hypoleptinemia may be partly compensated by engaging in frequent high-impact loading [5, 19]. There was no surprise to find FN BMD to be significantly greater in weight-loaded sport athlete group in this study. It has been shown previously that gymnastics training is beneficial to bone health in children and adolescents [4, 20]. In a cross-sectional study of prepubescent girls, Scerpella et al. [24] observed a dose-depended relationship between BMD and hours per week of gymnastics activity. Swimming as a non-weight-bearing sport is considered to be associated with lower BMD in athletes [3]. The difference between the groups with regard to the BMD at the spine was not as pronounced as at proximal femur most likely because FN BMD experiences greater mechanical loading during high-impact activities than LS BMD.

There are several shortcomings to this study. The cross-sectional design does not allow us to derive a cause-effect conclusion in this study and the sample size is relatively small. The use of DXA technology provides a static measure of bone density. In this study, bone biochemical markers were not used, but could have provided insights into more acute independent measures of bone status in relation to hormone markers. Our results provide some background information on evaluation of the relationship of IGF-1, estradiol and different adipocytokines with bone mineral variables in adolescent female athletes and untrained controls.

In summary, after adjustment for major confounders, FN and LS BMD correlated with concentrations of IGF-1, estradiol and leptin, as well as FN BMD with IGF-1/IGFBP-3 molar ratio, and FN BMC with IGF-1, IGF-1/IGFBP-3 molar ratio, and leptin in adolescent female athletes of weight-loaded sport only. The concentrations of visfatin, a fairly new adipocytokine, were not related to bone parameters in healthy adolescent girls with different training patterns. The FN BMD was significantly higher in weight-loaded athletes, supporting the benefits of regular weight-bearing physical activity during growth and maturation.

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