Effects of body composition, leptin and adiponectin on bone mineral density in prepubertal girls

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Effects of body composition, leptin and adiponectin on bone mineral density in prepubertal girls

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<ABSTRACT>

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The relationship between obesity and bone mineral density is not clear. Body weight is positively associated with bone mineral density. It has been a controversy whether lean mass or fat mass has more influence on bone stimulatory effect. Some adipokines seem to participate in bone metabolism. Leptin and adiponectin are potential independent contributors to bone mineral density. The aim of this study was to assess the relation among body composition, adipokines (leptin and adiponectin) and bone mineral density, and whether adipokines and body composition determine bone mineral density independently in prepubertal girls. Subjects included forty eight prepubertal girls. They were classified as obese and control groups according to their body mass index. Serum leptin and adiponectin levels were determined by enzyme immunoassay. Bone mineral density by dual energy X-ray absorptiometry and body composition by bioelectrical impedance analysis were measured. Lean mass was positively correlated with bone

mineral density. Fat mass was negatively correlated with L-spine bone mineral density after adjustment for body weight. Serum leptin levels were positively correlated with bone mineral density. Lean mass was a positive independent predictor of bone mineral density. Serum leptin was a positive independent predictor of femoral bone mineral density. Fat mass was found to be a negative independent predictor of femoral bone mineral density. Lean mass has favorable effect on bone mineral density. Fat mass seems not to be beneficial to the bone structure against osteoporosis, despite increased mechanical loading. Leptin may have a certain biological role in regulating bone metabolism.

Key words: bone mineral density, body composition, leptin, adiponectin, obesity

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I. INTRODUCTION

Rapidly increasing childhood obesity has become a major public health concern. Obesity is a main risk factor for cardiovascular disease, diabetes, hypertension and cancer[1-3]. However, the relationship between obesity and bone mineral density (BMD) is unclear[4].

Childhood and adolescence are the most important period for maximum bone mass acquisition, associated with genetic potential, nutritional factors, physical activity and body composition[5]. Osteoporosis-related fracture risk is highly dependent on BMD[6, 7]. Body weight is positively associated with BMD[8-10] and negatively associated with fracture incidence[7, 11]. However, it remains a controversy whether it is lean mass or adipose tissue that mediates the bone stimulatory effect exerted by weight[12-14]. Recent reports indicated that in young female populations, lean mass is a positive predictor[15, 16], whereas adipose tissue is a weaker positive[17], or a negative predictor of BMD[16, 18, 19]. Adipose tissue, once considered a metabolically passive fuel

depot for energy substrate, has recently become as a metabolically active tissue. It secretes a variety of proteins called adipokines into circulation, which play important roles in the modulation of biological functions. The relation between adipose tissue and BMD is credited not only to stress from mechanical loading but also to the metabolic effect of adipokines[20]. Leptin and adiponectin are potential contributors to BMD. Leptin is a satiety regulating hormone and have a central role not only regulating in energy expenditure, but also in bone metabolism[4]. Leptin increases the proliferation and differentiation of osteoblast in adults[21]. Adiponectin increases insulin sensitivity and may improve the lipid profiles[22, 23]. Serum adiponectin levels are negatively correlated with parameters of overall obesity[24]. It was suggested that high adiponectin levels may cause increased osteoclastic activity and low BMD[25]. Adiponectin, however, is also reported to increase osteoblastic activity and decrease osteoclastic activity in animals[26].

The relation between body composition, especially adipose tissue, and BMD in obese children is clinically important because any therapeutic interventions for obesity that modifies body composition may affect BMD and the risk of osteoporosis in later life. Few have attempted to investigate the effect of body composition and adipokines on BMD in children. Accordingly, I investigated the relation among body composition, leptin and adiponectin, and BMD, and whether adipokines and body composition determine BMD independently in prepubertal girls.

II. MATERIALS AND METHODS

1. Subjects

The Institutional Review Board at Korea University Ansan Hospital approved the study. Written informed consents were obtained from both subjects and parents. Forty eight children who visited department of pediatrics, Korea University Ansan Hospital due to obesity or non-endocrine disease participated in the study. All of the subjects were female and prepubertal. Pubertal stage was determined by a single pediatric endocrinologist according to the criteria of Tanner[27]. Children who showed pubertal development were excluded from the study. None of the subjects in this study had a medical history of cardiovascular disease, diabetes, hypertension and other endocrine disorders.

2. Anthropometric measurement

Height was measured to the nearest 0.1 cm using a rigid stadiometer. Weight was measured to the nearest 0.1 kg using a calibrated balance scale. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Among the forty eight subjects, twenty three (BMI $\geq$ 95th percentile for age and sex, according to 2007 Korean national growth chart) were classified into obese group and twenty five (25th percentile $\leq$ BMI < 75th percentile, according to 2007 Korean national growth chart) into control group.

3. Bone age assessment

A standard left-hand wrist radiograph was obtained and bone age was determined by a single observer according to Greulich and Pyle method[28], expressed in years.

4. Body composition assessment

Body composition measurement was performed by bioelectrical impedance analysis, using InBody 4.0 (Biospace, Seoul, Korea). Fat and lean mass were expressed in kilograms.

5. Bone mineral density assessment

BMD was measured by a single technician by way of dual energy X-ray absorptiometry (DXA), using Expert version 1.90 (Lunar Corp., Madison, WI, USA). BMD of L2-L4 lumbar spine and femoral neck was evaluated, expressed in gram/centimeter^2.

6. Biochemical assessment

Blood sampling was performed in the overnight fasting state. Serum insulin like growth factor-1 (IGF-1), insulin like growth factor binding protein-3 (IGFBP-3), luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, thyroid stimulating hormone (TSH), fT4, adrenocorticotropic hormone (ACTH), cortisol, parathyroid hormone (PTH), osteocalcin, insulin, glucose, total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, leptin and adiponectin were measured. Leptin levels were measured with enzyme immunoassay kit (ALPCO Diagnostics, Salem, NH, USA). Adiponectin levels were measured by enzyme immunoassay kit (AdipoGen, Inc., Seoul, Korea). Insulin resistance was estimated as homeostatic model assessment of insulin resistance (HOMA-IR), with the calculations as follows: HOMA-IR = [insulin (mU/l) x glucose (mmol/l)] / 22.5.

7. Statistical analysis

Data are expressed as mean ± SD. Anthropometric and endocrine characteristics were compared between obese and control groups using an independent t-test. Serum glucose, insulin, HOMA-IR, leptin, adiponectin levels, body composition and bone mineral density were compared between obese and control groups using an independent t-test. The relationship between BMD and other metabolic variables was determined by Pearson's correlation analysis and Partial correlation analysis. Multiple linear regression analysis was performed to investigate whether leptin, adiponectin, HOMA-IR and body composition determine BMD independently. The SPSS 12.0 software was used for statistical analysis. *P* values < 0.05 were considered statistically significant.

III. RESULTS

1. Anthropometric and endocrine characteristics

Anthropometric and endocrine characteristics of obese and control groups are shown in Table 1. LH, FSH and estradiol levels of all the subjects were less than 0.07 IU/l, 1.00 IU/l and 10.0 pg/ml, respectively. Obese group had significantly higher weight and BMI compared with control group. There was no significant difference in age, height, bone age, IGF-1, IGFBP-3, TSH, fT4, ACTH, cortisol, PTH, osteocalcin levels and lipid profiles between the two groups.

Table 1. Anthropometric and endocrine characteristics of obese and control groups

	Obese (n=23)	Control (n=25)	*P*
Age (year)	8.3 ± 1.3	8.7 ± 1.2	0.242
Height (cm)	133.5 ± 9.5	132.9 ± 10.1	0.819
Weight (kg)	40.5 ± 7.5	30.7 ± 7.0	<0.05
BMI (kg/m^2)	22.5 ± 1.9	17.2 ± 1.5	<0.05
Bone age (year)	10.5 ± 1.4	9.4 ± 1.1	0.194
IGF-1 (ng/ml)	349.3 ± 140.8	377.3 ± 168.3	0.537
IGFBP-3 (μg/ml)	3.49 ± 0.73	3.29 ± 0.81	0.378
TSH (mIU/l)	3.31 ± 1.79	1.82 ± 0.87	0.075
fT4 (ng/dl)	1.29 ± 0.18	1.34 ± 0.17	0.578
ACTH (pg/ml)	28.16 ± 15.47	23.02 ± 9.44	0.469
Cortisol (μg/ml)	13.15 ± 7.38	10.92 ± 4.99	0.516
PTH (pg/ml)	27.08 ± 17.76	28.90 ± 16.66	0.837
Osteocalcin (ng/ml)	68.06 ± 20.10	71.29 ± 15.46	0.735
Total cholesterol (mg/dl)	174.5 ± 23.9	172.8 ± 26.8	0.817
Triglyceride (mg/dl)	90.9 ± 47.3	95.3 ± 64.1	0.788
HDL-cholesterol (mg/dl)	51.7 ± 8.0	58.4 ± 14.5	0.056
LDL-cholesterol (mg/dl)	102.5 ± 20.9	93.0 ± 18.7	0.110

Data are shown as mean ± SD.

2. Serum glucose, insulin, leptin, adiponectin levels, body composition and bone mineral density

Serum glucose, insulin, leptin, adiponectin levels, body composition and bone mineral density of obese and control groups are shown in Table 2. Obese group had significantly higher serum leptin levels, fat mass, lean mass, femoral and L-spine BMD compared with control group. There was no significant difference in serum glucose, insulin, HOMA-IR and serum adiponectin levels between the two groups.

Table 2. Metabolic parameters, body composition and bone mineral density of obese and control groups

	Obese (n=23)	Control (n=25)	*P*
Glucose (mmol/l)	4.95 ± 0.29	5.02 ± 0.32	0.425
Insulin (mIU/l)	15.13 ± 5.19	11.18 ± 2.93	0.091
HOMA-IR	3.33 ± 1.24	2.40 ± 0.55	0.089
Leptin (ng/ml)	15.04 ± 7.13	6.34 ± 4.90	<0.05
Adiponectin (ng/ml)	10.06 ± 2.46	11.32 ± 2.45	0.081
Fat mass (kg)	13.8 ± 3.8	7.0 ± 2.4	<0.05
Lean mass (kg)	24.7 ± 4.1	20.2 ± 2.1	<0.05
BMD_{femur} (g/cm^2)	0.815 ± 0.098	0.665 ± 0.091	<0.05
$BMD_{L\text{-}spine}$ (g/cm^2)	0.789 ± 0.079	0.667 ± 0.071	<0.05

Data are shown as mean ± SD.

HOMA-IR: homeostatic model assessment of insulin resistance, BMD_{femur}: femoral bone mineral density, $BMD_{L\text{-}spine}$: L-spine bone mineral density.

3. Relationship of serum leptin, adiponectin levels, HOMA-IR and body composition with bone mineral density

The results of Pearson's correlation and Partial correlation after adjustment for body weight of serum leptin, adiponectin levels, HOMA-IR and body composition with bone mineral density are shown in Table 3. Body weight was positively correlated with femoral and L-spine BMD. Serum leptin, HOMA-IR, fat and lean mass had significant positive correlations with femoral BMD, and they disappeared after adjustment for body weight. Serum adiponectin was not correlated with femoral BMD. Serum leptin and lean mass had significant positive correlations with L-spine BMD, and still remained significant after adjustment for body weight. There was significant positive correlation between fat mass and L-spine BMD, but it became negative after adjustment for body weight. HOMA-IR and serum adiponectin level were not correlated with L-spine BMD.

Table 3. Correlation of metabolic parameters and body composition with bone mineral density

	BMD_{femur}		$BMD_{L\text{-}spine}$	
	Unadjusted	Body weight, adjusted	Unadjusted	Body weight, adjusted
Body weight	0.751*		0.761*	
Leptin	0.659*	0.128	0.481*	0.409*
Adiponectin	-0.181	0.025	-0.006	0.292
HOMA-IR	0.455*	0.080	0.353	-0.084
Fat mass	0.750*	-0.356	0.681*	-0.578*
Lean mass	0.818*	0.319	0.830*	0.490*

Pearson's correlation coefficients and Partial correlation coefficients after adjustment for body weight are presented.

BMD_{femur}: femoral bone mineral density, $BMD_{L\text{-}spine}$: L-spine bone mineral density, HOMA-IR: homeostatic model assessment of insulin resistance.

* $P<0.05$

4. Serum leptin, adiponectin levels, HOMA-IR and body composition as independent predictors of bone mineral density

The results of multiple linear regression analysis to investigate whether leptin, adiponectin and body composition determine BMD independently are shown in Table 4. Lean mass was found to be a positive independent predictor of femoral and L-spine BMD. Serum leptin was found to be a positive independent predictor of femoral BMD but not of L-spine BMD. Fat mass was found to be a negative independent predictor of femoral BMD but not of L-spine BMD. Serum adiponectin and HOMA-IR were not independent predictors of BMD.

Table 4. Serum leptin, adiponectin levels, HOMA-IR and body composition as independent predictors of bone mineral density

	BMD_{femur}		$BMD_{L\text{-}spine}$	
	β	*P*	β	*P*
Leptin	0.555	<0.05	-0.024	0.918
Adiponectin	-0.040	0.743	0.042	0.768
HOMA-IR	0.090	0.495	0.034	0.820
Fat mass	-0.593	<0.05	-0.109	0.740
Lean mass	0.979	<0.05	0.907	<0.05

Results of multiple linear regression analyses including serum leptin, adiponectin , HOMA-IR, fat and lean mass on bone mineral density. Standardized β and *P* values are presented.

BMD_{femur}:femoral bone mineral density, $BMD_{L\text{-}spine}$:L-spine bone mineral density, HOMA-IR:homeostatic model assessment of insulin resistance.

IV. DISCUSSION

In this study, I was able to demonstrate higher BMD in obese than control group children. This finding supports a positive relationship between body weight and BMD in the previous studies[8-10]. BMD of obese subject can be influenced by increased body weight. The bone structure can easily adapt to stimuli. Excessive weight produces a mechanical force on the bones, stimulating osteogenesis[29].

Obesity is characterized by increased body weight with excess body fat and a relative increase of lean mass. It has been a controversy whether lean mass or fat mass has more influence on bone stimulatory effect[12-14]. Previous studies indicated that regardless of age or gender, lean mass has a strong positive influence on BMD[17, 30, 31]. However, the results of previous studies on the relation between fat mass and BMD were conflicting. Adipose tissue is a weaker positive predictor[17] or even stronger predictor[10, 14] than lean mass, or even a negative predictor of BMD[18, 19].

This study indicates that lean mass is positively correlated with BMD and a positive independent predictor of BMD, whereas fat mass is negatively correlated with L-spine BMD after adjustment for body weight. This finding is consistent with previous reports suggesting that bone strengths is primarily determined by dynamic loads from muscle force, not static loads, such as fat mass[31]. I also found that fat mass was a negative independent predictor of femoral BMD after multiple linear regression analysis. It seems that the contribution of fat mass offset its potential benefit as a mechanical load. The basis for negative effect of fat mass on the bone mass observed in this study is unknown.

Adipose tissue is not a metabolically passive fuel depot for energy substrate anymore. It has become a metabolically active tissue, secreting a variety of adipokines that modulate biological functions. It is suggested that some

adipokines participate in bone metabolism. Leptin and adiponectin are potential contributors to BMD.

Leptin has been proposed to be a mediator of adipose tissue hormonal effect on bone mass[4]. The role of leptin in bone metabolism is not fully understood, but animal studies showed the 'high bone mass phenotype' in the leptin deficient mice[32]. In humans, some studies[4, 33, 34] have failed to show any association between serum leptin levels and BMD in women or in men, whereas others have reported a positive association between leptin and BMD[35]. In a few recent studies[36, 37], leptin was negatively correlated with BMD. In this study, I showed that serum leptin levels were positively correlated with both femoral and L-spine BMD, and leptin was an independent positive predictor of femoral BMD.

Adiponectin acts directly on bone to induce human osteoblast proliferation and differentiation, and to increase osteoclast formation indirectly[25, 38]. Another previous study[39] showed that adiponectin exerted a negative independent effect on BMD. Some studies also reported that there were no independent relationship between adiponectin and BMD[40, 41]. I was not able to show any correlation between adiponectin and BMD.

Another link between obesity and BMD is insulin. Insulin reduces the hepatic synthesis of sex hormone carriers. Thus, there is an increase in free form sex hormones, which stimulates the activity of osteoblasts[42]. I found that HOMA-IR had a weak positive correlation with femoral BMD, but no significant correlation with L-spine BMD.

This study was limited to prepubertal girls to control other factors that affect BMD. In puberty, growth hormone and sex steroid actively participate in the bone structure development as a result of normal growth[5]. Sex seems to be an important determinant of BMD, probably because of different muscle and sex steroid level in boys and girls[43].

It should be noted that this cross sectional study limits the interpretation of

the results, especially with regard to cause-effect interactions. Another limit of this study is the fact that we did not include male and pubertal subject and I did not control the life style of subjects such as calcium diet and exercise.

In conclusion, in prepubertal girls, lean mass has favorable effect on BMD. Lean mass is a positive independent predictors of femoral and L-spine BMD. Fat mass is a negative independent predictor of femoral BMD. Fat mass seems not to be beneficial to the bone structure against osteoporosis, despite increased mechanical loading. Leptin can predict femoral BMD independently. Leptin may have a certain biological role in regulating bone metabolism. Further prospective study including male and pubertal subjects is necessary to apply our findings to general populations.

V. CONCLUSION

I assessed the effects of body composition, leptin and adiponectin on bone mineral density in prepubertal girls. Lean mass is more favorable to the bone mass than fat mass against osteoporosis. Leptin may have a certain biological role in regulating bone metabolism.

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< ABSTRACT (IN KOREAN) >

사춘기이전 여아에서 체성분, 렙틴, 아디포넥틴의 골밀도에 대한 영향

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비만과 골밀도의 상관 관계는 명확하지 않다. 체중은 골밀도와 양의 상관 관계가 있다. 그러나, 제지방과 체지방 중 어느 것이 골밀도에 더 영향을 끼치는지에 대해서는 논란의 여지가 많다. 어떤 지방세포에서 분비되는 호르몬은 골대사에 직접 관계되는 것으로 보인다. 렙틴과 아디포넥틴은 골밀도에 독립적으로 영향을 주는 것으로 보인다. 본 연구의 목적은 체성분과 렙틴, 아디포넥틴의 골밀도에 대한 영향을 알아보고, 체성분과 렙틴, 아디포넥틴이 골밀도에 독립적인 영향을 주는지 확인해 보는 것이다. 대상 환아는 모두 48명의 사춘기 이전 여아로 구성되었다. 이들은 체질량지수에 의해 비만군과 대조군으로 분류되었다. 혈중 렙틴, 아디포넥틴 농도를 효소면역 측정법으로 측정하였다. 체성분은 생체전기 임피던스법으로, 골밀도는 이중 에너지 방사선 흡수법으로

측정하였다. 제지방은 골밀도와 양의 상관 관계가 있었다. 체지방은 체중을 통제한 후 요추 골밀도와 음의 상관 관계가 있었다. 혈중 렙틴 농도는 골밀도와 양의 상관 관계가 있었다. 제지방은 골밀도에 대해 독립적인 양의 예측자로 판명되었다. 혈중 렙틴 농도는 대퇴 골밀도에 대한 독립적인 양의 예측자였다. 체지방은 대퇴 골밀도에 대한 독립적인 음의 예측자였다. 제지방은 골밀도에 유익한 영향을 끼치며, 체지방은 물리적인 부하에도 불구하고 골밀도에 유익하지 않는 것으로 보인다. 렙틴은 골대사의 조절에 특정한 생물학적 역할을 하는 것으로 생각된다.

핵심되는 말: 골밀도, 체성분, 렙틴, 아디포넥틴, 비만