Leptin to adiponectin ratio at the age of 12 is negatively associated with lumbar spine bone mineral apparent density independently of body fat mass in 18-year old males

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Background

Inconsistent associations of leptin and adiponectin with bone mineral characteristics in puberty and adolescence have been reported. The leptin to adiponectin ratio (LAR) has proven a more accurate marker of obesity-related complications than adiponectin or leptin alone (1).

Aim

To examine associations between leptin to adiponectin ratio (LAR) in puberty and bone mineral characteristics at 18 years of age and increase of bone mineral characteristics until 18 years of age.

Subjects

- 88 boys were studied at baseline (T1) at the mean age of 12.1 years (range 10.6–13.4), at the mean of 14.0 years (12.5-15.3) at T2 and at 18.0 years (16.5-19.2) at T3 (Table 1).
- Anthropometry was measured and blood samples were obtained at all three time points (T1, T2 and T3) of the study. Bone age and sexual maturation were studied at T1 and T2. Bone mineral characteristics, body composition and physical activity were studied at T1 and T3.

Methods

Physical activity

Physical activity (PA) was measured objectively by Actigraph accelerometer (GT1M ActiGraph, Monrovia, CA, USA) for seven consecutive days during the wake up time. Total daily physical activity (tot PA) was calculated as the total number of counts divided by the registered time (counts/min).

Bone Mineral Density (BMD)

Total body (TB) BMD (g/cm^2) and lumbar spine (LS) BMD (g/cm^2) and bone area (BA) were measured by DEXA scan aDPX-IQ (Lunar Corporation, Madison,WI) at T1 and by DEXA scan Discovery (Hologic QDR Series, Waltham, MA, USA) at T2.

Bone mineral apparent density (BMAD) (g/cm^3), an estimate of volumetric bone density, was calculated using a formula of TB BMAD=TB BMC/(TB BA^2/height) and a formula of LS BMAD=LS BMC/(BA$^{1.5}$). The precision of measurement expressed as coefficient of variation was <2% for all bone mineral measurements.

To adjust BMD characteristics measured by different DEXA scans at different study points, SDS were calculated for TB BMAD and LS BMAD at T1 and T2: SDS BMAD = [an individual BMAD at T1 (or T2) – mean BMAD of total group at T1 (or T2)]/ SD of total group at T1 (or T2). The change in SDS (Δ) of BMAD from T2 to T1 was calculated: BMAD SDS at T2 - BMAD SDS at T2.

Blood Analyses

Venous blood samples were obtained after an overnight fast between 8:00 $_{AM}$ and 9:00 $_{AM}$, the blood serum was separated and then frozen at −80 °C for further analysis. Leptin concentration was determined by radioimmunoassay (Mediagnost GmbH, Reutlingen, Germany), adiponectin with a commercially available radioimmunoassay kit (Linco Research, St. Charles, MO) and total testosterone (nmol/L) and insulin using Immulite® 2000 (DPC, Los Angeles, USA). Glucose was measured with a commercial kit (Boehringer, Mannheim, Germany). The estimate of insulin resistance by homeostasis model assessment (HOMA-IR) was calculated: fasting serum insulin (μU/mL) × fasting serum glucose (mmol/L)/22.5.

Statistical Analyses

Statistical analyses were performed using SPSS software version 20.0 for Windows (SPSS, Inc., Chicago, IL). To compare our study population with the external reference population, age-adjusted Z-scores for total body less head (TB LH) BMD and LS BMD were calculated at T3 using the prediction equations and reference standards by Crabtree et al (2). Leptin and adiponectin measurements were log transformed and mean pubertal LAR calculated: (LAR at T1 + LAR at T2)/2. Partial correlation analysis was performed to assess the relationships of BMD with mean pubertal LAR, with total body fat percentage, HOMA-IR, total testosterone and total PA at T1 included as covariates. P-value of less than 0.05 was considered significant for both analyses.

Results

Table 1. Clinical characteristics, blood markers, physical activity data and bone mineral characteristics at different time points of the study. Median with 25th and 75th percentile for adipokine data, HOMA-IR and physical activity data and mean SD for all other characteristics are shown.

		Time point		
Variable		T1	T2	T3
Clinical characteristics				
	Age (y)	12.1±0.7	14.0±0.7*	18.0±0.7*†
	Body mass (kg)	47.2±12.7	59.61±13.7*	73.9±12.1*†
	Body height (m)	1.55±0.08	1.69±0.8*	1.81±0.07*†
	BMI (kg/m2)	19.5±4.0	20.60±3.74*	22.4±3.3*†
	Total body fat %	23.15±10.54		18.07±4.92*
Blood markers				
	Leptin (ng/ml)	3.40 (1.8;9.99)	2.3 (0.6;5.65)*	1.85 (0.68;3.36)* †
	Adiponectin (μg/ml)	7.7 (5.0;11.1)	6.2 (4.5;9.2)*	3.27 (2.64;4.03)*†
	Leptin to adiponectin ratio	0.46 (0.18;1.37)	0.22 (0.10;0.94)*	0.48 (0.19;1.03)†
	HOMA-IR	1.69 (1.15;2.68)	2.35 (1.76;3.24)*	1.40 (1.04;1.84)*†
	Testosterone (nmol/L)	4.81±5.65	13.59±6.22*	20.23±5.24*†
Physical activity data				
	Total PA (counts/min)	434 (359; 573)	350 (283; 497) *	380 (303; 498) *†
Bone mineral characteristics				
	TB BMD (g/cm^2)	0.98±0.07		1.23±0.09*
	LS BMD (g/cm^2)	0.83±0.09		1.06±0.10*
	TB LH BMC (g)	1341.7±337.8		2323.04±358.01*
	LS BMC (g)	27.41±6.77		58.44±9.34*
	TB BMAD (g/cm^3)	0.088±0.006		0.095±0.005*
	LS BMAD (g/cm^3)	0.147±0.013		0.143±0.013*
	BMC/height	1110.26±181.62		1590.14±188.91*

HOMA-IR, homeostasis model assessment-insulin resistance; PA, physical activity; TB, total body; BMD,bone mineral density; LS, lumbar spine; LH, less head; BMC, bone mineral content; BMAD, bone mineral apparent density.
* Significantly different (p < 0.05) from T1; † significantly different (p < 0.05) from T2.

MAIN FINDING

Mean pubertal LAR was negatively correlated with:

- LS BMD at T3 (r = -0.311; p < 0.05)
- LS BMAD at T3 (r = -0.405; p < 0.05)
- Δ LS BMD SDS (r = -0.397; P <0.05)
- Δ LS BMAD SDS (r = -0.415; P <0.05).

when controlling for total body fat %, total testosterone, HOMA-IR and physical activity at T1 in partial corrrelation analysis.

Conclusions

Leptin to adiponectin ratio (LAR) in puberty is negatively associated with lumbar spine BMD and BMAD increment in puberty and lumbar spine BMD and BMAD at the age of 18.

References

1. Inoue M, Yano M, Yamakado M, Maehata E, Suzuki S. Relationship between the adiponectin-leptin ratio and parameters of insulin resistance in subjects without hyperglycemia. Metabolism (2006) 55:1248–54.
2. Crabtree NJ, Shaw NJ, Bishop NJ, Adams JE, Mughal MZ, Arundel P, Fewtrell MS, Ahmed SF, Treadgold LA, Högler W, et al. Amalgamated reference data for size-adjusted bone densitometry measurements in 3598 children and young adults—the ALPHABET study. J Bone Miner Res (2017) 32:172–80.