

Important Links between Fat Derived Proteins and Bone Remodeling Factors in Lean and Obese Girls

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INTRODUCTION

Fat and bone are linked by a multitude of pathways supporting a skeleton appropriate for the mass of adipose tissue of the organism. Insulin, leptin, adiponectin and estrogens are all likely to be involved in this connection. Among them the fat-cell derived hormone leptin significantly contributes to bone health.

Leptin binds to the leptin receptor inhibiting bone formation and promoting bone absorption. Furthermore, it inhibits the secretion of the receptor activator of the NF- κ B ligand (RANKL) by osteoblasts by stimulating the production of osteoprotegerin (OPG) and up-regulating the OPG/RANKL balance¹.

The main biological function of OPG is to neutralize RANKL and control the formation, activity, and survival of osteoclasts, so that bone absorption is inhibited.

In this context we aimed to investigate the relations of adipose tissue hormones, such as leptin, adiponectin, RBP-4 and lipocalin-2, along with the low grade inflammation marker hs-CRP, with markers of bone metabolism such as OPG, RANKL, osteocalcin, C-terminal cross-linking telopeptide of collagen type-I (CTX), bone alkaline phosphatase (bALP) and tartrate-resistant acid phosphatase isoform-5b (bone TRACP-5b) in girls with various degrees of BMI.

SUBJECTS AND METHODS

➤ Eighty girls (age 9–15 years) were enrolled in the study divided by their BMI standard deviation scores (BMI-SDSs) into 4 groups of 20 girls each: overweight 1.8 ± 0.4 ; obese 2.2 ± 0.4 ; morbidly obese 3.6 ± 0.4 and lean controls -0.11 ± 0.4 . The subjects' characteristics are summarized in Table 1.

➤ Blood Chemistry parameters determined:

- ✓ Glucose and insulin (calculation of HOMA index);
- ✓ Adiponectin, leptin, retinol binding protein-4 (RBP-4) and lipocalin-2 (NGAL);
- ✓ Osteoprotegerin (OPG), receptor activator of NF- κ B ligand (RANKL), osteocalcin, C-terminal cross-linking telopeptide of collagen type-I (CTX), bone alkaline phosphatase (bALP) and tartrate-resistant acid phosphatase isoform-5b (bone TRACP-5b) and
- ✓ hs-CRP.

All specific proteins were measured by means of immunoenzymatic, electrochemiluminescence and nephelometric assays.

RESULTS

The main results of the study are summarized in Table 2 and showed that: a) OPG, RANKL and bALP levels decreased significantly as BMI-SDSs increased ($r = -0.307$, $r = -0.301$ and $r = -0.307$ respectively, $p < 0.01$), while osteocalcin, CTX and bone TRACP5 show no relations ($p > 0.60$); b) leptin correlated negatively with bALP, bone TRACP-5b, osteocalcin, OPG (Figure 2) and RANKL ($r = -0.342$, $r = -0.248$, $r = -0.258$ and $r = -0.310$ respectively, $p < 0.05$); adiponectin correlated positively with CTX and OPG ($r = 0.316$, $p = 0.004$ and $r = 0.237$, $p = 0.04$, respectively); RBP-4 correlated positively with OPG and bALP ($r = 0.290$, $p < 0.01$ and $r = 0.336$, $p = 0.002$, respectively), while lipocalin-2 correlated positively with bALP ($r = 0.454$, $p < 0.001$); c) obesity-related systemic inflammation expressed as hs-CRP correlated negatively only with OPG ($r = -0.308$, $p = 0.007$).

Table 2. Blood Chemistry Data.

	Controls	Overweight	Obese	morbidly-obese
Fasting glucose (mg/dL)	84(2)	81(1)	84(2)	82(2)
Fasting insulin (mIU/L)	11.6(1.7)	14.4(1.4)	15.4(1.5)	18.6(2.1)
HOMA index	1.99(0.4)	2.89(0.3)	3.06(0.4)	3.41(0.4)
Total Cholesterol (mmol/L)	4.1(0.6)	4.3(0.7)	4.5(0.8)	4.2(1.0)
Triglycerides (mmol/L)	0.6(0.2)	1.0(0.4)	1.0(0.7)	0.8(0.2)
HDL-C (mmol/L)	1.3(0.2)	1.3(0.5)	1.2(0.2)	1.1(0.2)
LDL-C (mmol/L)	2.5(0.6)	2.6(0.5)	2.6(0.5)	2.7(1.0)
Leptin (μ g/L)	13.3(2.1)	32.1(3.4)	34.2(3.1)	55.4(5.3)
Adiponectin (mg/L)	8.7(0.6)	7.9(0.6)	5.9(0.6)	6.5(0.4)
RBP4 (mg/L)	24.8(1.3)	27.0(1.1)	24.9(1.4)	19.6(1.0)
Lipocalin-2 (μ g/L)	23.3(4.6)	17.5(3.1)	12.2(1.7)	16.3(3.7)
bALP (U/L)	62.4(43.4)	44.9(39.4)	50.7(36.3)	25.1(36.3)
TRACP-5b (U/L)	2.2(1.2)	2.2(1.2)	2.2(1.2)	1.6(0.9)
CTX (ng/L)	1.8(0.6)	1.7(0.7)	1.6(0.5)	1.8(0.5)
Osteocalcin (μ g/L)	86.2(26.2)	75.7(32.4)	75.2(30.2)	73.3(24.6)
OPG (ng/L)	4.7(1.1)	3.9(1.2)	3.9(0.8)	3.4(1.2)
RANKL (ng/L)	0.8(0.8)	0.4(0.5)	0.4(0.4)	0.5(0.4)
hs-CRP (mg/L)	0.43(0.1)	1.20(0.3)	1.81(0.3)	2.19(0.3)

Table 1: Patients' Family History and Clinical Profile

	Controls	Overweight	Obese	Morbidly-obese
Number	20	20	20	20
Sex	Female	Female	Female	Female
BMI-SDS	-0.11(0.4)	1.8(0.4)	2.2(0.4)	3.6(0.4)
Age (years, range)	9.0-14.0	9.0-14.5	9.0-16.0	8.9-14.0
1st degree relative with obesity only (%)	0/20	0/20	1/20	5/20
1st degree relative with obesity and DM type 2 (%)	1/20	1/20	1/20	3/20
2 nd degree relative with DM type 2 (%)	4/20	5/20	11/20	13/20
Tanner Stage	3/17	3/17	3/17	2/18
Pre-/Post menarche	9/11	9/11	10/10	9/11

Tanner Stage BI= Breast Tanner Stage I, BII= Breast Tanner Stage II to V.

Figure 1.

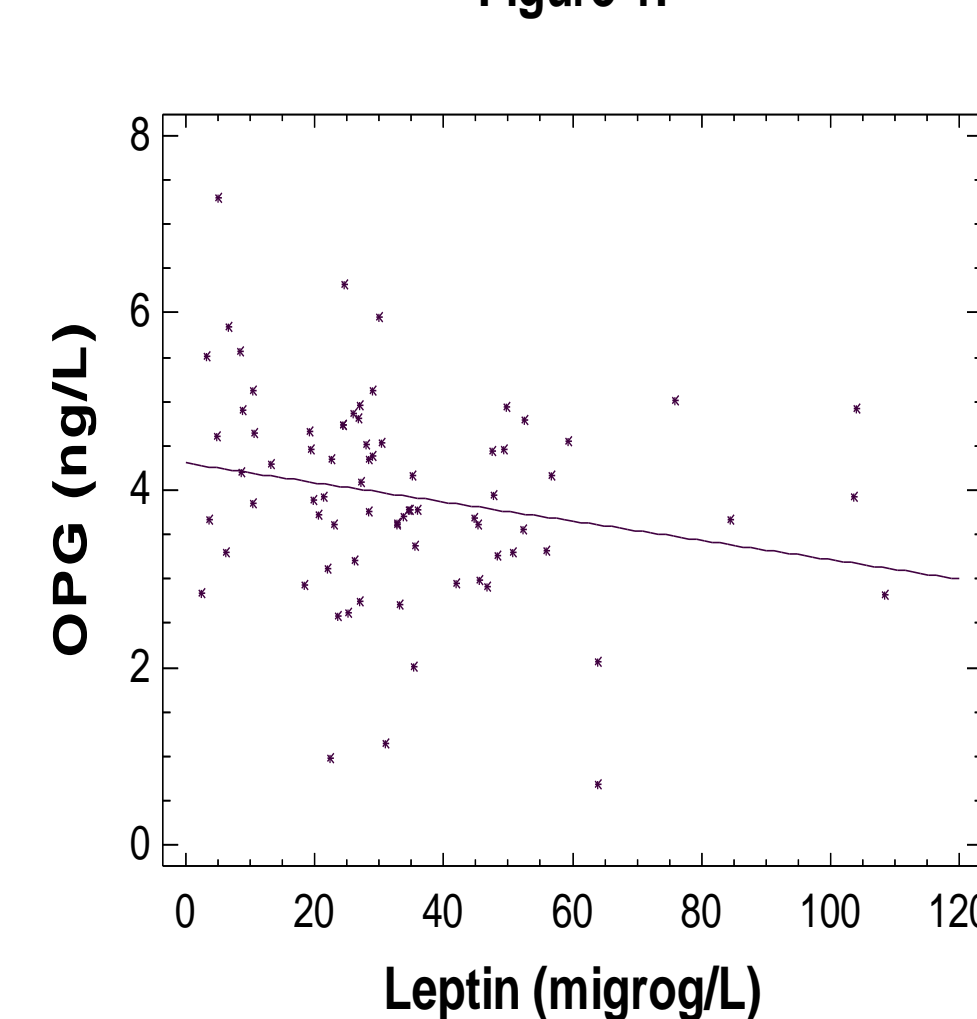


Figure 2.

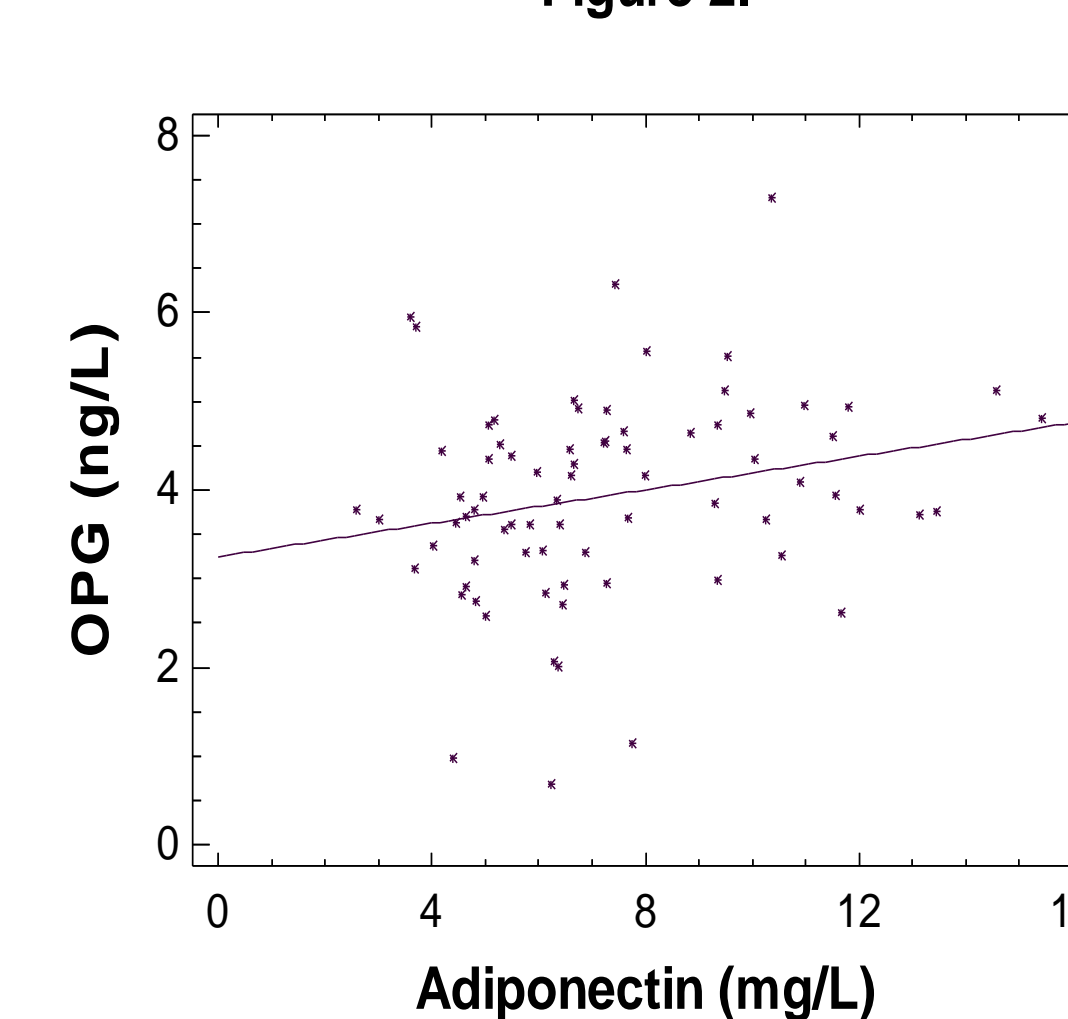
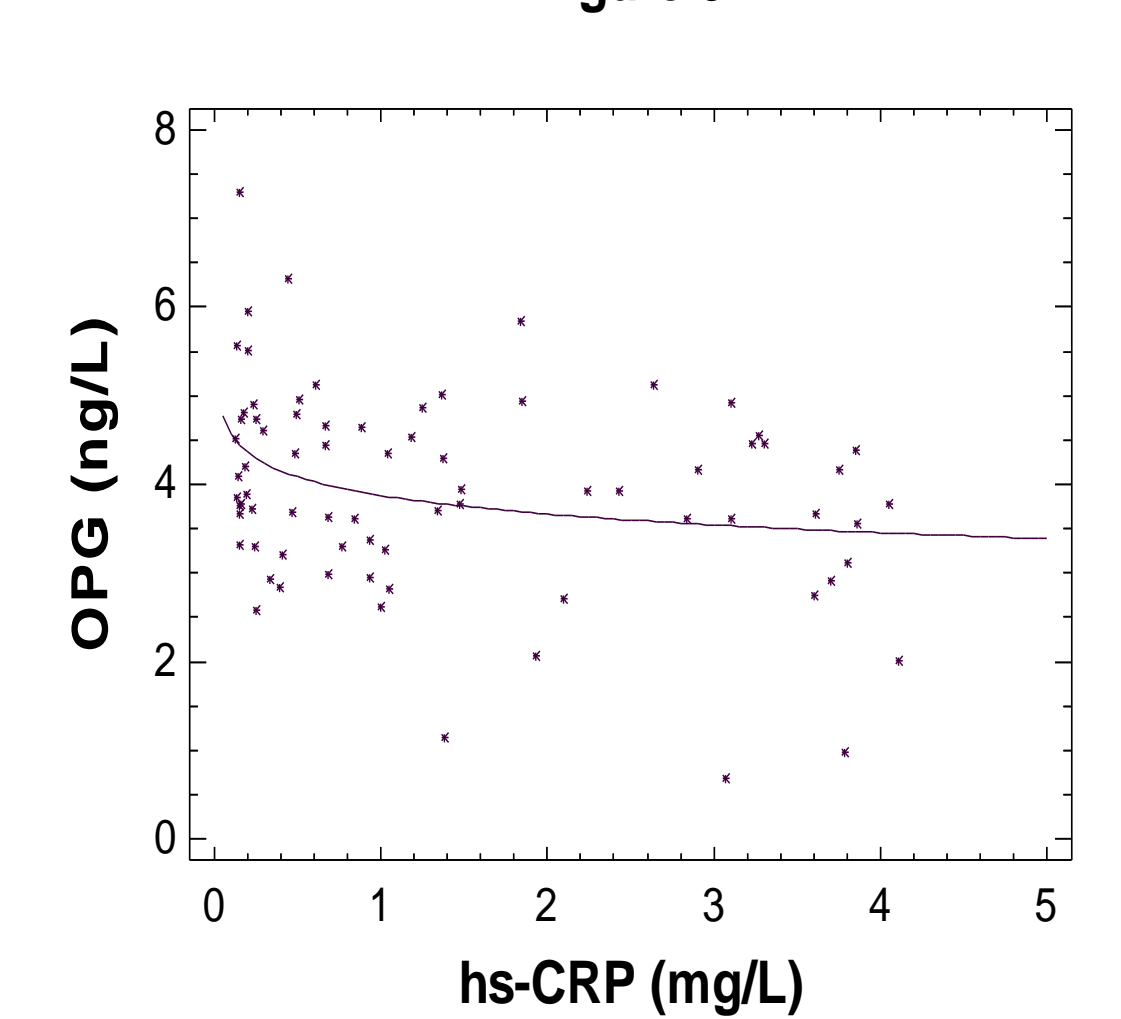


Figure 3



CONCLUSIONS

Our findings suggest that there are important links between adipose tissue-derived proteins and bone remodeling factors. Bone turnover was altered in obese girls mainly due to decreased OPG levels. There were significant correlations of OPG with leptin, adiponectin and hs-CRP, indicating that, probably, the bone mass is regulated by adipokines, as well as by low grade inflammation in obese children.

¹Dimitri et al. Bone 50: 457–466, 2012.

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