A Link between Bone Mineral Density and Serum Adiponectin and Visfatin Levels in Acromegaly

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Context: Two adipokines highly expressed in fat mass, adiponectin with antiinflammatory and antiatherogenic properties and visfatin with an insulin-mimetic effect, are potential contributors to bone metabolism. In acromegaly, data on adiponectin are contradictory, and there are no data on visfatin.

Objectives: The aim of the study was to evaluate adiponectin and visfatin in acromegaly, compared to control subjects, and to analyze their relationship with body composition and bone markers.

Methods: Bone markers [osteocalcin, total amino-terminal propeptide of type 1 procollagen (total P1NP), carboxy-terminal telopeptide (β-Crosslaps)], body composition (by dual-energy x-ray absorptiometry), adiponectin (by ELISA), and visfatin (by immunoanalysis) were evaluated in 60 acromegalic patients (24 males and 36 females) and in 105 age- and gender-matched healthy controls (33 males and 72 females). Acromegalic patients were classified as controlled, with normal IGF-I and nadir GH no greater than 1 μg/liter (n = 41), or active (n = 19).

Results: Acromegalic patients had lower adiponectin (P < 0.01), more lean body mass (P < 0.01), more total body mass (P < 0.01), higher bone formation markers (osteocalcin and total P1NP, P < 0.05 and P < 0.01, respectively), but less bone resorption markers (β-Crosslaps, P < 0.001) than controls. No differences in visfatin and BMD were found between patients and controls. Adiponectin correlated negatively with BMD (r = −0.374; P < 0.05) and lean mass (r = −0.301; P < 0.05) and positively with age (r = 0.341; P < 0.001) in acromegaly. Visfatin correlated negatively with BMD (r = −0.359; P < 0.05). BMD was the predictor for adiponectin and visfatin.

Conclusions: Acromegalic patients present hypoadiponectinemia and a favorable bone marker profile. Adiponectin and visfatin could be a link between fat mass and bone in acromegaly. (J Clin Endocrinol Metab 94: 3889–3896, 2009)
dyslipidemia, essential hypertension, coronary heart disease, and insulin-resistant states, such as type 2 diabetes, lipodystrophy, and metabolic syndrome (5–10). Adiponectin is also negatively correlated with bone mineral density (BMD) in the general population, suggesting a further link between fat mass (FM) and bone (11). Because obesity and body fat are directly related to BMD, an association between adipocyte-dependent hormonal factors and bone has been hypothesized (12, 13). In acromegaly, a few reports regarding adiponectin have been published with contradictory results. Lam et al. (14) found low adiponectin levels in patients with active disease (when FM is decreased due to the lipolytic effect of GH), reversible after treatment, but other studies found no correlation between adiponectin levels and cardiovascular risk or insulin resistance in acromegalic patients (15, 16). To our knowledge, no data regarding adiponectin and BMD in acromegaly have been reported.

Visfatin is a novel adipokine, predominantly secreted by visceral adipose tissue. Although questions on its assay specificity have been raised, an insulin-mimetic effect by activating insulin receptors has been put forward, and it is elevated in diabetes and central obesity (17). No data investigating visfatin in acromegaly or its potential effects on bone mass have been reported to date, to our knowledge.

Although adiponectin and visfatin have recently been described as potential contributors to bone metabolism, their precise roles have not been fully elucidated. It has been reported that adiponectin may have a protective effect on bone metabolism in patients with type 2 diabetes mellitus (18). The aim of this study is to evaluate adiponectin and visfatin and their relationship with body composition parameters and bone mineral markers in acromegaly.

Subjects and Methods

Subjects

This case-control study included 60 acromegalic patients (24 males and 36 females, diagnosed and treated in our center since 1982 and who agreed to participate) and 105 healthy controls (33 males and 72 females, selected from the blood donor database at our hospital and matched for age, gender, and date of blood donation [the same year as the diagnosis of acromegaly]).

A single doctor (N.S.) updated the clinical history and performed a physical examination, including anthropometric measurements, in both patients with acromegaly and healthy controls. Metabolic syndrome was defined according to Adult Treatment Panel III criteria (19) and required the presence of three or more of the following: waist circumference greater than 88 cm in women and greater than 102 cm in men; triglyceride level of at least 150 mg/dl; high-density lipoprotein cholesterol in men below 40 mg/dl and in women below 50 mg/dl; fasting glucose of at least 110–125 mg/dl; and systolic/diastolic blood pressure of at least 130/85 mm Hg or self-reported use of antihypertensive medications.

Whole body dual-energy x-ray absorptiometry (DEXA) scanning and fasting blood sampling [including fasting plasma glucose, fasting insulinemia, GH, IGF-I, adiponectin, visfatin, osteocalcin, carboxy-terminal telopeptide (β-Crosslaps) and total type 1 amino-terminal propeptide of procollagen (total P1NP)] were performed. Biochemical control of acromegaly was defined as GH levels below 1 μg/liter basally or during a 2-h 75-g oral glucose tolerance test and normal age- and sex-matched IGF-I; patients who did not attain these levels were considered active. An oral glucose tolerance test was performed postoperatively (within 2 months after surgery) if a discrepancy between basal GH and IGF-I was present and in active patients on somatostatin analog treatment if IGF-I levels were equivocal. In controlled patients, and also diabetic patients, basal GH and IGF-I were used to evaluate disease activity in follow-up. All patients and controls signed an informed consent after study approval by the hospital ethics committee. At the time of the study, of the 60 acromegalic patients studied, 54 had undergone surgery (53 transsphenoidal and one craniotomy), three received conventional radiotherapy as the first definitive treatment, and three “naïve” subjects were waiting for transsphenoidal surgery.

At the time of the study, GH hypersecretion persisted in 19 (active patients), of which 16 were treated with somatostatin analogs, two with pegvisomant, and one was on combination therapy with both drugs. The remaining 41 were controlled (as defined above) without medical treatment.

Body composition analysis

Lumbar spine and whole body BMD and body composition [lean body mass (LBM), whole body and truncal FM, and total mass] were measured by DEXA scanning (Delphi QDR 4500; Hologic, Vilvoorde, Belgium). The coefficient of variation (CV) for BMD was 1%.

Biochemical measurement

Blood samples were collected after an overnight fast. Glycated hemoglobin measurement was performed by an immunoturbidimetric method. Insulin was determined by solid-phase, enzyme-labeled chemiluminescent immunometric assay (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA). Insulin resistance was calculated using the formula of the homeostasis model assessment (HOMA) = [insulin (μU/ml) × glucose (mmol/liter)]/22.5. Serum GH was determined by a chemiluminescence system (Immulite; EURO/Diagnostic Products Corporation, Llanberis, UK) which uses the human GH 80/505 calibrator with a sensitivity of 0.01 μg/liter (conversion factor for SI units, μg/liter × 2.6 = mIU/liter) and with intraassay CV of 5.3–6.5%. Serum IGF-I concentration was determined by solid-phase, enzyme-labeled chemiluminescent immunometric assay (Immulite 2000; Diagnostic Products Corp., Los Angeles, CA) with a sensitivity of 20 μg/liter and a total imprecision of 3.7–8.1%. In the study, IGF-I is expressed as SD score (SDS). Serum samples for adiponectin and visfatin were promptly separated and stored at −80°C until assayed. Adiponectin was determined by ELISA (EZHADP-61K; Promocell GmbH, Heidelberg, Germany) with an intraassay CV of 3.4% and an interassay CV of 5.7%. Serum visfatin concentrations were measured by an enzyme immunoassay (Phoenix Peptides, Karlsruhe, Germany).
with an intrassay CV of less than 5%, and an interassay CV of less than 14%. Bone biochemical markers were measured: osteocalcin and total P1NP as bone formation markers, and β-Crosslaps as a bone resorption marker. Osteocalcin was measured by enzyme-labeled chemiluminescent immunometric assay (Immulate 2000, Siemens Medical Solutions Diagnostics Ltd., Llanberis, UK), with an imprecision for mean concentrations between 4.0 and 47.3  μg/liter of 3.2–4.8%. β-Crosslaps and total P1NP were measured by electrochemiluminescent immunoassay (Elecsys Modular Analytics E170; Roche Diagnostics GmbH, Mannheim, Germany) with an imprecision for mean concentrations between 0.08 and 3.19  μg/liter of 1.0–4.6% for β-Crosslaps and between 29.1 and 1027  μg/liter of 1.1–2.9% for total P1NP.

**Results**

**Morbidity, body composition, and bone resorption markers: differences between groups**

No differences in age, body mass index, waist circumference, or the prevalence of hypogonadism between the 60 acromegalic patients and 105 controls were observed (52.5 ± 13.1 vs. 50.8 ± 11.6 yr; 27.8 ± 3.7 vs. 27.5 ± 5 kg/m²; 97.4 ± 12.4 vs. 99.1 ± 16.3 cm; and 61.6 vs. 53.1%, respectively). Patients with acromegaly had more diabetes mellitus (23.2 vs. 2.4%; *P < 0.001*), hypertension (37.7 vs. 15%; *P < 0.005*), and metabolic syndrome (25.4 vs. 10.8%; *P < 0.05*) than controls. No differences were found in the prevalence of dyslipidemia (30 vs. 24.7%), obesity (23.4 vs. 20%), or smoking (26.4 vs. 19.4%). The prevalence of hypogonadism was lower in active acromegalic patients than in controlled patients (42.1 vs. 70.7%; *P < 0.05*), probably related to their difference in age.

Table 1 summarizes the results of adiponectin, visfatin, and body composition. Acromegalic patients had less adiponectin (*P < 0.01*) and more LBM (*P < 0.01*) and total body mass (*P < 0.01*) than controls (Table 1). Active acromegalic patients had less adiponectin and total and trunk FM (*P < 0.001*), but more LBM (*P < 0.001*) and more BMD (*P < 0.05*) than controlled patients (Table 1). No differences were found in visfatin groups. Patients had higher osteocalcin and total P1NP (bone formation markers) but less β-Crosslaps, a bone resorption marker, than controls (Fig. 1).

When comparing diabetic (*n* = 12) and nondiabetic acromegalic patients, diabetics were older (62.5 ± 7.9 vs.
Correlations in acromegaly and controls

Correlations between adiponectin, visfatin, nadir GH, IGF-I SDS, bone formation (osteocalcin and total P1NP) and resorption markers (β-Crosslaps) and body composition parameters in the acromegalic patients (controlled and active together and separately) and in controls are shown in Table 2.

Adiponectin correlated negatively with BMD in controlled acromegalic patients and healthy controls, but not in patients with active disease in whom a positive correlation was found for total FM (r = 0.627; P < 0.05) and trunk FM (r = 0.552; P < 0.05) and adiponectin.

In the whole acromegaly cohort and especially in those with active disease, a significant correlation was found between osteocalcin and fasting glucose. Disease activity (expressed as IGF-I SDS) in acromegalic patients was correlated with β-Crosslaps and P1NP, but interestingly, no correlation was observed with osteocalcin and IGF-I SDS (Table 2).

When studying only diabetic acromegalic patients (n = 12), BMD and adiponectin correlated negatively with glucose (r = −0.711, P < 0.05; and r = −0.744, P < 0.05, respectively) and glycated hemoglobin (r = −0.874, P = 0.01; and r = −0.782, P < 0.05, respectively). No further correlations were found between adiponectin, visfatin, bone markers, glucose metabolism profile, and body composition parameters.

Regression analysis

In a multiple linear stepwise regression analysis, BMD was shown to be the predictor for adiponectin (r = 0.37; P < 0.01) and visfatin (r = 0.24; P < 0.05) in acromegalic patients.

Discussion

Acromegalic patients have an increased cardiovascular risk, and cardiovascular disease is the leading cause of mortality (20), despite having a decreased body FM and increased LBM (21–23). Therefore, factors other than increased FM must contribute to explaining the higher cardiovascular risk. Among others, new adipocyte-related hormones could play a role in this risk.

Adiponectin, a protein secreted by the adipose tissue, regulates energy homeostasis and has antiatherogenic and antiinflammatory properties; it is significantly reduced in obesity compared with controls, as well as in type 2 diabetes mellitus, dyslipidemia, essential hypertension, metabolic syndrome, and coronary artery disease (5, 24) and increases after massive weight loss (25, 26). It has been suggested that the degree of hypoadiponectinemia was more closely related to the degree of insulin resistance than to the degree of adiposity (2). Gender also influences adiponectin levels, with women having higher concentrations than men (27). The role of adiponectin in acromegaly is not well-established (14, 15). Lam et al. (14) reported a reversible decrease of adiponectin in active acromegalic patients showing that hypoadiponectinemia, reversible with GH-lowering therapies, may contribute to the increased insulin resistance and cardiovascular risk, but other studies did not confirm this, suggesting a possible permissive role of GH and IGF-I excess on adiponectin secretion (15, 16). Acromegaly is associated with a high prevalence of diabetes and hyperinsulinemia (which reduces adiponectin), but also with a reduction in FM (which in normal population and different metabolic diseases increases adiponectin). In our study, acromegalic patients had more diabetes and metabolic syndrome and less FM and adiponectin levels compared with controls. The low adiponectin levels could be explained by the lower FM in acromegalic patients, in particular in those with active disease. Indeed, in this later situation, we observed a significant correlation between adiponectin and FM, not observed in controls or in acromegalic patients with controlled disease, where the main correlations were seen with BMD and age. An explanation could be that the marked reduction in body fat determined by excess GH/IGF-I determines a fall in the synthesis of adiponectin, which is no longer correlated with BMD. Because low adiponectin is an independent cardiovascular risk factor (28), it can be
TABLE 2. Correlations between adiponectin, visfatin, IGF-I SDS, nadir GH, and body composition parameters in acromegalic patients and controls

<table>
<thead>
<tr>
<th>Adiponectin</th>
<th>BMD, r = −0.374; P &lt; 0.05</th>
<th>BMD, r = −0.303; P &lt; 0.05</th>
<th>BMD, r = −0.458; P &lt; 0.05</th>
<th>Total FM, r = 0.627; P &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBM, r = −0.301; P &lt; 0.05</td>
<td>BMD, r = −0.227; P &lt; 0.05</td>
<td>Age, r = 0.388; P &lt; 0.05</td>
<td>Trunk FM, r = 0.552; P &lt; 0.05</td>
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<tr>
<td>Age, r = 0.347; P &lt; 0.001</td>
<td>Visfatin, r = −0.290; P &lt; 0.05</td>
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</table>

<table>
<thead>
<tr>
<th>Visfatin</th>
<th>BMD, r = −0.359; P &lt; 0.05</th>
<th>BMD, r = −0.354; P &lt; 0.01</th>
<th>BMD, r = −0.456; P &lt; 0.001</th>
<th>Nadir GH, r = 0.604; P &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteocalcin, r = 0.422; P &lt; 0.05</td>
<td>IGF-I SDS, r = 0.560; P &lt; 0.001</td>
<td>IGF-I SDS, r = 0.575; P &lt; 0.01</td>
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<td>Trunk FM, r = 0.769; P &lt; 0.05</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>Age, r = 0.394; P &lt; 0.01</td>
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<tr>
<td>Fasting glucose, r = 0.270; P &lt; 0.05</td>
<td>Total FM, r = 0.388; P &lt; 0.01</td>
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<tr>
<td>β-Crosslaps</td>
<td>Total FM, r = −0.294; P &lt; 0.05</td>
<td></td>
<td>IGF-I SDS, r = 0.549; P &lt; 0.05</td>
<td></td>
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<tr>
<td>Trunk FM, r = −0.354; P &lt; 0.01</td>
<td></td>
<td></td>
<td>Fasting glucose, r = 0.760; P &lt; 0.001</td>
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<tr>
<td>IGF-I SDS, r = 0.560; P &lt; 0.001</td>
<td></td>
<td></td>
<td>IGF-I SDS, r = 0.549; P &lt; 0.05</td>
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<tr>
<td>Total P1NP</td>
<td>Trunk FM, r = −0.316; P &lt; 0.01</td>
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<td></td>
<td>Fasting insulinemia, r = 0.671; P &lt; 0.05</td>
</tr>
<tr>
<td>Trunk FM, r = −0.316; P &lt; 0.01</td>
<td>IGF-I SDS, r = 0.520; P &lt; 0.001</td>
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<tr>
<td>BMD</td>
<td>Total FM, r = −0.361; P &lt; 0.01</td>
<td>Total FM, r = −0.332; P &lt; 0.01</td>
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<tr>
<td>Trunk FM, r = −0.341; P &lt; 0.05</td>
<td>Trunk FM, r = −0.243; P &lt; 0.05</td>
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<tr>
<td>LBM, r = 0.283; P &lt; 0.05</td>
<td>LBM, r = 0.447; P &lt; 0.001</td>
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<tr>
<td>Nadir GH</td>
<td>Trunk FM, r = −0.329; P &lt; 0.05</td>
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<tr>
<td>IGF-I SDS</td>
<td>Total FM, r = −0.495; P &lt; 0.001</td>
<td></td>
<td></td>
<td>LBM, r = 0.444; P &lt; 0.01</td>
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<tr>
<td>Trunk FM, r = −0.432; P &lt; 0.001</td>
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<tr>
<td>LBM, r = 0.428; P &lt; 0.001</td>
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IGF-I is expressed as SDS.

added to the general and specific cardiovascular risk of acromegalic patients.

Regarding body composition, controversy still exists as to whether BMD is increased or not in these patients (29–31); furthermore, BMD is not a reliable marker of bone fragility in acromegaly, and osteoporotic fractures may occur even in the presence of normal bone mass (32). Our previous study (33) showed that acromegaly affected bone mass differently in males and females; in males, active disease increased BMD and bone mineral content, which normalized with disease control. However, in acromegalic females, neither activity nor hypogonadism seemed to determine BMD or bone mineral content. To our knowledge, no association between BMD and adiponectin in acromegaly has been reported previously. In this study, adiponectin correlated negatively with BMD in controlled acromegalic patients and normal controls, but not in active disease, where the marked fall in body fat was associated with a decrease in adiponectin. Furthermore, in the linear multiple regression analysis, BMD was a predictor of serum adiponectin and visfatin levels.

Although in the general population, in both genders, an association between adiponectin and decreased BMD (11, 13, 34–36) and an increase in bone formation markers (11, 13) have been reported, suggesting a hormonal link between adiposity or body mass and bone metabolism, other reports did not find the same result (12) or even
showed that adiponectin induced osteoblast formation and differentiation (37). Recently, a link between adiponectin and bone homeostasis has been reported by demonstrating transcription, translation, and secretion of adiponectin, as well as expression of its receptors, AdipoR1 and AdipoR2, in bone-forming cells. Adiponectin and the receptors are expressed in primary human osteoblasts from femur and tibia (37). Supplementation of culture medium with recombinant adiponectin enhances the proliferation of murine osteoblasts (37). Adiponectin was also found to stimulate receptor activator for nuclear factor κB ligand and inhibit osteoprotegerin expression in human osteoblasts through the MAPK signaling pathway (38). The regulation and detailed function of adiponectin in bone still remains obscure, but these findings point to a functional role in bone homeostasis, where adiponectin would provide a signal linking fat and body weight to bone density (37).

Visfatin is another protein secreted predominantly by visceral adipose tissue that mimics insulin actions. Visfatin does not decrease uniformly after weight loss, suggesting that the improvement in the low-grade inflammatory state described in obesity cannot be explained only in terms of a reduction of visceral FM (24). In our study, visfatin was negatively correlated with BMD in acromegalic patients and positively with FM only in active disease. To our knowledge, no previous studies have reported visfatin levels in acromegalic patients and/or its correlations with BMD. Although there is controversy on the relevance and real meaning of circulating visfatin, the closest correlations were found precisely between visfatin and fat \( r = 0.769 \) for trunk and \( r = 0.799 \) for total FM, higher than those found for adiponectin \( r = 0.627 \) for total FM. There were also moderately high correlations between visfatin and nadir GH \( r = 0.604 \) and IGF-I SDS \( r = 0.575 \), but only in controlled patients; this may imply that the known lipolytic effect of active acromegaly occurs once GH and/or IGF-I rise, but it is not related to the degree of activity of the disease.

Our results demonstrate an increase in bone formation and a decrease in resorption markers in acromegaly, especially in active disease compared with normal controls. Indeed, this would support prior suggestions that bone turnover markers could be useful in the evaluation of disease activity in acromegaly (21, 39). Although BMD did not differ in the whole acromegaly cohort when compared with controls, patients with active disease did have a greater BMD than those with controlled disease. The significant correlations of disease activity (as expressed by the IGF-I SDS) with both \( \beta \)-Crosslaps and P1NP would support a causal effect of acromegaly on bone metabolism. Finally, the negative correlation of BMD with body fat and positive correlation of BMD with LBM, together with BMD being a predictor for adiponectin and visfatin, implies cross-talk between fat, LBM, and bone.

In humans, osteocalcin appears to mediate the role of bone as an endocrine organ and is postulated to be an active regulator of insulin sensitivity by bone, and its main predictor is visceral fat (40, 41). Our findings that BMD is a predictor of adiponectin would support such a metabolic role for this cytokine, osteocalcin being a “bone hormone” that acts on FM. Reduced osteocalcin has been described in diabetes (40, 42, 43). In our study, circulating osteocalcin in acromegalic patients doubled that of controls, despite a 10 times higher prevalence of diabetes in acromegaly (23 vs. 2.4%), and active acromegaly also exhibited osteocalcin concentrations which doubled that of controlled patients. Furthermore, a correlation was found between osteocalcin and fasting glucose, especially in patients with active disease. This would imply a probable role for osteocalcin not only in bone metabolism but also for that of glucose and fat, and it may further link bone and adipose tissue. In acromegaly, the hyperglycemic effect of excess GH may prevail over the insulin-sensitizing effect of osteocalcin, demonstrated in the general population, or as IGF-I has been demonstrated to activate the osteocalcin promoter, it is possible that the effects of IGF-I on osteocalcin override the putative homeostatic mechanisms involved in the osteocalcin-insulin axis (44).

In conclusion, acromegalic patients present an unfavorable metabolic profile (diabetes mellitus, hypertension, and metabolic syndrome), hypoadiponectinemia, and changes in body composition (reduced FM and increased total mass and LBM). BMD is correlated negatively with, and is a predictor for, adiponectin and visfatin, suggesting that these adipokines could be a link between FM and bone in acromegaly. The emerging possible role of osteocalcin deserves further investigation. More specific studies devoted to unraveling and understanding this “communication” between bone and fat present a new challenge for the endocrinologist in the field of metabolic disorders.

Acknowledgments

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This work was supported by Grant FIS05/0448 from Instituto Carlos III and an unrestricted grant from Pfizer, Spain. A poster on this work was presented at the 2008 Annual Meeting of The Endocrine Society in San Francisco, California. E.R. was the recipient of one of the poster prizes.

Disclosure Summary: The authors have nothing to disclose.


