Elevated Peptide YY Levels in Adolescent Girls with Anorexia Nervosa

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Background: Peptide YY (PYY) is an intestinally derived anorexigen that acts via the Y2 receptor, and Y2 receptor deletion in rodents increases bone formation. Anorexia nervosa (AN) is associated with a deliberate reduction in food intake and low bone density, but endocrine modulators of food intake in AN are not known. In addition, known regulators of bone turnover such as GH, cortisol, and estrogen, explain only a fraction of the variability in bone turnover marker levels.

Hypotheses: We hypothesized that PYY may be elevated in AN compared with controls and may contribute to decreased food intake and bone formation.

Methods: Fasting PYY was examined in 23 AN girls and 21 healthy adolescents 12–18 yr old. We also examined GH, cortisol, ghrelin, and leptin (overnight frequent sampling) and fasting IGF-I, estradiol, total T3, and bone markers. Macronutrient intake and resting energy expenditure (REE) were measured.

Results: AN girls had higher PYY levels compared with controls (17.8 ± 10.2 vs. 4.8 ± 4.3 pg/ml; P < 0.0001). Predictors of log PYY were nutritional markers, including body mass index (r = −0.62; P < 0.0001), fat mass (r = −0.55; P = 0.0003), and REE (r = −0.51; P = 0.0006), and hormones, including GH (r = 0.38; P = 0.004) and T3 (r = −0.59; P = 0.0001). Body mass index, fat mass, REE, GH, and T3 explained 68% of the variability of log PYY. Log PYY predicted percentage of calories from fat (r = −0.56; P = 0.0002) and independently predicted osteocalcin (r = −0.45; P = 0.003), bone-specific alkaline phosphatase (r = −0.46; P = 0.003), N-telopeptide/creatinine (r = −0.55; P = 0.0003), and deoxyypyridinoline/creatinine (r = −0.52; P = 0.001) on regression modeling.

Conclusion: Elevated PYY may contribute to reduced intake and decreased bone turnover in AN. (J Clin Endocrinol Metab 91: 1027–1033, 2006)
dent studies have demonstrated an increase in bone formation after selective deletion of the hypothalamic-specific Y2 receptor (20). However, a relationship between PYY and bone turnover markers has not been explored. AN in adolescents is associated with low bone density and reduced bone turnover (21, 22) and is a useful model in which to examine the relationship between PYY and bone turnover markers.

We hypothesized that decreased food intake in AN may be associated with elevated PYY levels, and that PYY would be an independent predictor of the reduced bone turnover observed in this population. We therefore compared PYY levels in adolescent girls with AN with healthy adolescents to determine whether elevations in PYY in AN may exert an anorexigenic effect, resulting in decreased food intake. We also determined nutritional and hormonal predictors of PYY and the relationship between PYY and bone turnover markers.

**Subjects and Methods**

**Subject selection**

Twenty-three adolescent girls with AN (diagnosed by Diagnostic and Statistical Manual of Mental Disorders-IV criteria) [chronological age, 16.2 ± 1.6 yr; bone age (BA), 15.8 ± 1.5 yr] and 21 healthy girls of comparable chronological age (15.4 ± 1.8 yr) and maturity (BA, 15.7 ± 2.1 yr) were examined. Baseline characteristics, but not PYY values, food intake, and resting energy expenditure (REE), have been reported previously (17, 18, 23). Duration of illness was 7.9 ± 10.4 months in girls with AN. Methods of recruitment included referrals from eating disorders units in the New England area for girls with AN and mass mailings to pediatricians, nutritionists, and psychiatrists, as well as within the Partners HealthCare system. The study was approved by the Partners Institutional Review Board, and informed assent and consent were obtained from all subjects and their parents.

**Experimental protocol**

Subjects were admitted for an overnight stay at the General Clinical Research Center of Massachusetts General Hospital after a screening visit to rule out thyroid dysfunction, premature ovarian failure, and hyperprolactinemia. All enrolled subjects had a hematocrit greater than 35%, potassium greater than 3 mmol/liter and glucose levels more than 70 mg/dl. Height was measured in triplicate on a single stadiometer at 30%, potassium greater than 3 mmol/liter and glucose levels more than 70 mg/dl. Height was measured in triplicate on a single stadiometer at 30%

Subjects underwent frequent sampling for GH, cortisol, leptin, and ghrelin overnight between 2000 and 0800 h, which has been reported previously (10, 12, 23, 24). In this paper, we have used area under the curve (AUC) for these hormones and nadir GH concentrations [from Cluster analysis (25)]. Fasting blood samples were obtained for PYY, glucose, insulin, IGF-I, total T₄s, and estradiol. BA was determined in all subjects using an x-ray of the left wrist and hand with the methods of Greulich and Pyle (26). Bone density and body composition were measured by dual-energy x-ray absorptiometry (model no. 4500; Hologic, Waltham, MA). We measured three serum markers of bone formation, namely carboxy-terminal propeptide of type I collagen (PICP), osteocalcin (OC), and bone-specific alkaline phosphatase (BSAP), and two urinary markers of bone resorption [N-telopeptide (NTX) and deoxypyridinoline (DPD), normalized for creatinine levels] as reported previously in Refs. 10, 12, 23, and 24.

Nutrient intake was determined from food diaries (3 weekdays and 1 weekend day) using NDS-R software (version 4.03; nutrient database 31; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). REE was determined by indirect calorimetry (Vmax 29N; SensorMedics, Loma Linda, CA) (27, 28). Subjects sat quietly in a thermal neutral room for at least 15 min before indirect calorimetry. Oxygen consumption and carbon dioxide production were measured continuously.

Subjects with AN were followed for a 1-yr period and examined again at weight recovery (defined as a 10% increase in BMI). PYY levels at weight recovery were available in 10 girls with AN.

**Biochemical assessment**

PYY was measured using a human PYY (3–36) RIA (Phoenix Pharmaceuticals, Belmont, CA), with 100% cross-reactivity with the two biologically active forms of PYY (1–36 human PYY and 3–36 human PYY) and no cross-reactivity with NPY, pancreatic polypeptide, insulin, glucagon, amylin amide, or substance P. Intraassay coefficient of variation of the assay is 5.6%, and the lower limit of detection was 2.8 pg/ml. Glucose levels were measured by the hospital laboratory using published methods (29). RIA was used to measure serum cortisol (Diagnostic Products, Los Angeles, CA) (limit of detection, 1 μg/dl; sensitivity, 0.21 μg/dl; coefficient of variation, 2.5–4.1%), leptin (Linco Diagnostics, St. Charles, MO) (sensitivity, 0.5 ng/ml; coefficient of variation, 3.4–8.3%), insulin (Linco Diagnostics) (sensitivity, 2 μU/ml; coefficient of variation, 2.2–4.4%), ghrelin (Phoenix Pharmaceuticals) (sensitivity, 2 pg/tg; coefficient of variation, 10%), total T₄s (DiaSorin, Stillwater, MN) (sensitivity, 9.0 ng/dl; coefficient of variation, 3.1–7.9%), and estradiol (Diagnostic Systems Laboratories, Webster, TX) (limit of detection, 2.2 pg/ml; coefficient of variation, 6.5–8.9%). An immunoradiometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA) was used to measure GH (detection limit, 0.05 ng/ml; intraassay coefficient of variation, 2.4–9.4%) and IGF-I (detection limit, 30 ng/ml; coefficient of variation, 3.1–4.6%). PICP was measured using an RIA (DiaSorin) (limit of detection, 25 ng/ml; coefficient of variation, 1.3–3.8%), and OC was measured using an immunoradiometric assay (Nichols Institute Diagnostics) (sensitivity, 0.5 ng/ml; coefficient of variation, 3.2–5.2%). BSAP was measured using an ELISA (Quidel, Mountain View, CA) (sensitivity, 0.7 U/liter; coefficient of variation, 3.9–5.8%). We measured urine DPD and NTX in a 2-h, second morning urine sample normalized for creatinine excretion. DPD and NTX were also measured by ELISAs (Quidel, Inc. (minimum detection limit, 1.1 nmol/liter; coefficient of variation, 4.3–8.4%) and Ostex International, Inc. (Seattle, WA; detection limit, 20 nmol bone collagen equivalent; intraassay coefficient of variation, 5–19%)). Urine creatinine was measured by the hospital laboratory using published methods. Samples were stored at –80°C until analysis. All samples were run in duplicate.

Glucose levels can be converted to SI units (millimoles per liter) by dividing by 18. Levels of GH, IGF-I, and leptin can be converted to SI units (micrograms per liter) by multiplying by 1, and serum cortisol can be converted to SI units (nanomoles per liter) by dividing by 0.0363. Homeostasis model of assessment of insulin resistance (HOMA-IR) was used as a measure of insulin resistance (30) and was calculated using the following formula: [fasting glucose (millimoles per liter) × fasting insuline (microunits per milliliter)]/22.5.

**Statistical analysis**

All data are presented as mean ± sd. Data were analyzed using the JMP program (version 4; SAS Institute, Cary, NC). The Student’s t test was used to calculate differences between means. When data were not normally distributed, logarithmic conversions were performed to approximate a normal distribution, in particular for PYY. Wilcoxon’s rank-sum test was used to compare ghrelin AUC in AN and controls because lognormal and other conversions were not successful in approximating a normal distribution.

Univariate regression analyses followed by mixed model stepwise regression analyses (P = 0.15 for entry into the model and P = 0.10 to leave the model) were used to determine predictors of PYY, food intake, and bone turnover markers. Covariates used to predict PYY levels were based on data from available literature (BMI, fat mass, GH, IGF-I, thyroid hormones, and ghrelin) (3, 17, 19), and we also examined the relationship between PYY and other hormones, such as cortisol and leptin, and with REE, which provides an assessment of required calorie intake. Variables used to predict food intake included hormones that affect appetite, namely PYY, leptin, ghrelin, cortisol, and thyroid hormones. For bone turnover markers, our choice of covariates included PYY based on a rodent study in which Y2 receptor deletions led to an
increase in osteoblastic activity (20) and other nutritional and hormonal markers known to affect bone metabolism based on our previous studies (31). Outlier analysis was performed, and, based on a rule of three sds from the mean, values for bone turnover markers for one subject were excluded from analysis.

Results

Clinical characteristics

Clinical characteristics of our subjects are summarized in Table 1. Macronutrient intake and REE are reported in Table 2. Girls with AN had lower z-scores at the lumbar spine (−0.71 ± 0.94 vs. −0.24 ± 0.80; \( P = 0.05 \)) and hip (−0.26 ± 1.34 vs. 0.47 ± 1.1; \( P = 0.05 \)) than controls.

PYY

PYY levels were significantly higher in girls with AN than in controls (17.8 ± 10.2 vs. 4.8 ± 4.3 pg/ml; \( P < 0.0001 \)), as were log PYY levels (1.19 ± 0.24 vs. 0.57 ± 0.32 pg/ml; \( P < 0.0001 \)) (Fig. 1). Logarithmic conversion of PYY values was necessary to approximate normal distribution of data. Weight recovery (10% increase in BMI) in 10 girls with AN was associated with a trend toward a decrease in PYY values (15.1 to 9.2 pg/ml; \( P = 0.08 \)) and log PYY values (1.13 to 0.88 pg/ml; \( P = 0.07 \)) on paired t test analysis in the weight-recovered group (Fig. 2).

Predictors of PYY

Univariate analyses. Log PYY levels correlated inversely with BMI (\( r = -0.62; P < 0.0001 \)), fat mass (\( r = -0.55; P = 0.0003 \)), and REE (\( r = -0.51; P = 0.0006 \)) in the group as a whole. In addition, log PYY correlated inversely with HOMA-IR (\( r = -0.59; P = 0.0002 \)), leptin AUC (\( r = -0.57; P = 0.0001 \)), total T3 (\( r = -0.59; P = 0.0001 \)), and IGFI (\( r = -0.53; P = 0.0004 \)).

Log PYY correlated positively with GH nadir concentration (\( r = 0.38; P = 0.004 \)), cortisol AUC (\( r = 0.44; P = 0.004 \)), and ghrelin AUC (\( r = 0.34; P = 0.03 \)). Figure 3 demonstrates some of these associations.

Regression modeling. On stepwise multiple regression modeling with significant predictors from univariate analyses entered into the model, significant and independent predictors of log PYY were BMI (\( P < 0.0001 \)), fat mass (\( P = 0.02 \)), nadir GH (\( P = 0.02 \)), total T3 (\( P = 0.04 \)), and REE (\( P = 0.046 \), contributing to 44.4, 6.0, 6.9, 6.5, and 4.0% of the variability, respectively (accounting for 67.9% of the variability in log PYY).

Predictors of macronutrient intake

Univariate analyses. Log PYY predicted fat intake (\( r = -0.44; P = 0.006 \)) (Fig. 4), percentage of calories derived from fat (\( r = -0.56; P = 0.0002 \)), and percentage of calories derived from carbohydrates (\( r = 0.54; P = 0.0004 \)). In addition, total T3 predicted fat intake (\( r = 0.42; P = 0.006 \)), percentage of calories derived from fat (\( r = 0.56; P = 0.0002 \)), and percentage of calories derived from carbohydrates (\( r = -0.54; P = 0.0004 \)). Other predictors of macronutrient intake were leptin AUC (\( r = 0.48, P = 0.001 \) for fat intake; \( r = 0.42, P = 0.006 \) for percentage of calories from fat; \( r = -0.36, P = 0.026 \) for percentage of calories from proteins) and cortisol AUC (\( r = -0.32, P = 0.04 \) for fat intake).

Regression modeling. On regression modeling with log PYY, total T3, cortisol AUC, and leptin AUC entered into the model, log PYY was an independent predictor of fat intake, percentage of calories derived from fat, and percentage of calories from carbohydrates, contributing to 51.3, 31, and 29% of the variability, respectively. Total T3 contributed another 5.7% to the variability in percentage of calories from fat and leptin AUC to 23.1% of the variability in total fat intake. On further adjustment for BMI, log PYY remained the most significant predictor of percentage of calories derived from fat and carbohydrates (31 and 29% of the variability).

Predictors of bone markers

Univariate analyses. Log PYY correlated inversely with all markers of bone turnover except PICP (OC, \( r = -0.45, P = 0.003 \); BSAP, \( r = -0.46, P = 0.003 \); NTX/creatinine, \( r = -0.55, P = 0.0003 \); DPD/creatinine, \( r = -0.52, P = 0.001 \)). We have demonstrated previously that important hormonal predictors of bone turnover markers and bone density in this group include GH AUC, cortisol AUC, and estradiol (31).

Table 1. Clinical characteristics of adolescent girls with AN and healthy adolescents

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 21)</th>
<th>AN (n = 23)</th>
<th>( P )</th>
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<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>21.7 ± 3.6</td>
<td>16.7 ± 1.2</td>
<td>&lt;0.0001</td>
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<tr>
<td>Fat mass (kg)</td>
<td>17.4 ± 1.0</td>
<td>8.8 ± 0.9</td>
<td>&lt;0.0001</td>
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<td>HOMA-IR</td>
<td>3.05 ± 0.93</td>
<td>1.36 ± 0.61</td>
<td>&lt;0.0001</td>
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<tr>
<td>Fasting IGFI (ng/ml)</td>
<td>531 ± 153</td>
<td>315 ± 141</td>
<td>&lt;0.0001</td>
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<tr>
<td>GH AUC (ng/ml per 12 h)</td>
<td>2,596 ± 1,112</td>
<td>3,879 ± 2,007</td>
<td>0.01</td>
</tr>
<tr>
<td>GH nadir (ng/ml)</td>
<td>1.03 ± 0.91</td>
<td>2.28 ± 1.40</td>
<td>0.001</td>
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<tr>
<td>Cortisol AUC (µg/dl per 12 h)</td>
<td>4,117 ± 802</td>
<td>6,112 ± 1,467</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ghrelin AUC (µg/ml per 12 h)</td>
<td>374,758 ± 174,020</td>
<td>457,421 ± 157,984</td>
<td>0.02</td>
</tr>
<tr>
<td>Leptin AUC (ng/ml per 12 h)</td>
<td>11,439 ± 4,752</td>
<td>3,417 ± 2,574</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total T3 (ng/ml)</td>
<td>1.54 ± 0.49</td>
<td>0.87 ± 0.20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>21.9 ± 8.8</td>
<td>16.7 ± 6.6</td>
<td>0.03</td>
</tr>
<tr>
<td>PICP (mg/ml)</td>
<td>225 ± 124</td>
<td>165 ± 68</td>
<td>0.05</td>
</tr>
<tr>
<td>OC (ng/ml)</td>
<td>45.9 ± 29.5</td>
<td>33.6 ± 17.2</td>
<td>0.10</td>
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<tr>
<td>BSAP (U/liter)</td>
<td>42.3 ± 33.0</td>
<td>27.8 ± 18.3</td>
<td>0.08</td>
</tr>
<tr>
<td>NTX/creatinine (nmol BCE/mmol creatinine)</td>
<td>162 ± 142</td>
<td>100 ± 57</td>
<td>0.06</td>
</tr>
<tr>
<td>DPD/creatinine (nmol/mmol creatinine)</td>
<td>14.1 ± 13.6</td>
<td>8.8 ± 3.3</td>
<td>0.09</td>
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</table>

BCE, Bone collagen equivalents. Mean ± SD.

* Wilcoxon’s rank-sum test.
Other important predictor was BMI (12.6% of the variability; P<0.002) toward a decrease in PYY values. Although it is uncertain and total T3 also predicted PYY levels. PYY in turn predicted including BMI and fat mass, and by REE. GH concentration PYY in adolescent girls with AN compared with controls. AN had higher log PYY levels than controls. healthy adolescents of comparable maturity (P<0.05), and, for DPD/creatinine, the most significant predictor of levels of OC, BSAP, NTX/creatinine, in addition to log PYY, significant predictors were BMI and cortisol AUC (27.0 and 5.3% of the variability, respectively; P=0.003, 0.003, 0.0003, and 0.007). The other significant predictor of OC and BSAP levels in this larger model was GH AUC (additional 7.9 and 5.0% of variability, respectively; P=0.05 and 0.10). For NTX/creatinine, in addition to log PYY, significant predictors were BMI and cortisol AUC (27.0 and 5.3% of the variability; P=0.002 and P=0.05), and, for DPD/creatinine, the other important predictor was BMI (12.6% of the variability; P=0.02).

**Discussion**

We report for the first time significantly higher levels of PYY in adolescent girls with AN compared with controls. Levels of PYY were predicted by nutritional markers, including BMI and fat mass, and by REE. GH concentration and total T3 also predicted PYY levels. PYY in turn predicted fat intake, and weight recovery was associated with a trend toward a decrease in PYY values. Although it is uncertain whether appetite is indeed suppressed in AN or whether appetite signals from the hypothalamus are overcome by signals from other areas of the brain, it is possible that decreased food intake in AN may be a consequence of anorexigenic effects of high levels of PYY. In addition, we observed that PYY was an important predictor of most bone turnover markers, such that high levels of PYY were associated with low levels of these markers, suggesting that PYY may have effects on bone metabolism. Of note, these are correlational studies that demonstrate associations but do not imply causation, and interventional studies are necessary to confirm our findings.

Our data differ from recently reported studies in girls with AN (1) and women with bulimia nervosa (18), in which PYY values were not significantly different from controls. Both of these studies examined a smaller number of subjects than our study, and lack of power may have accounted for the absence of a statistically significant difference between the groups. Our data are consistent with studies in obesity, which have reported lower PYY values than in controls (3, 32, 33), suggesting that, in overweight conditions, low PYY levels may lead to increased food intake, whereas in AN, high PYY levels may contribute to a decrease in food intake. Girls with AN had marked reductions in fat intake in our study, consistent with reports from other investigators (34), and indeed, strong negative associations were noted between fasting PYY levels and fat intake. Of note, administration of PYY to obese individuals results in a decrease in food intake (3). Effects of PYY differ from those of other hormones affecting appetite such as leptin, which is anorexigenic, and ghrelin, which is orexigenic, in that in obesity and AN, there appears to be a resistance to the effects of leptin and ghrelin but not to the

**Table 2. Nutrient intake in healthy adolescent girls and girls with AN**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 21)</th>
<th>AN (n = 23)</th>
<th>P</th>
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<tbody>
<tr>
<td>Caloric intake (cal)</td>
<td>1775 ± 495</td>
<td>1496 ± 606</td>
<td>0.10</td>
</tr>
<tr>
<td>Fat intake (g)</td>
<td>59.8 ± 17.6</td>
<td>36.6 ± 19.4</td>
<td>0.0002</td>
</tr>
<tr>
<td>Protein intake (g)</td>
<td>61.5 ± 19.0</td>
<td>66.5 ± 27.0</td>
<td>0.50</td>
</tr>
<tr>
<td>Carbohydrate intake (g)</td>
<td>255.3 ± 88.1</td>
<td>237.0 ± 97.7</td>
<td>0.52</td>
</tr>
<tr>
<td>% calories from fat</td>
<td>30.7 ± 6.3</td>
<td>21.7 ± 6.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% calories from protein</td>
<td>14.1 ± 2.9</td>
<td>18.0 ± 3.8</td>
<td>0.0007</td>
</tr>
<tr>
<td>% calories from carbohydrates</td>
<td>56.8 ± 7.9</td>
<td>63.9 ± 7.4</td>
<td>0.004</td>
</tr>
<tr>
<td>REE (cal)</td>
<td>1323 ± 270</td>
<td>975 ± 242</td>
<td>&lt;0.0001</td>
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</table>

**Fig. 1.** Log PYY levels in adolescent girls with AN (gray bar) and healthy adolescents of comparable maturity (white bar). Girls with AN had higher log PYY levels than controls.

**Fig. 2.** PYY values at baseline and weight recovery (10% increase in BMI) in 10 girls with AN. A trend toward a decrease in PYY levels was observed with weight recovery. Seven of these 10 girls with AN had a decrease in PYY values, whereas only 3 of the 10 showed some increase in PYY values.

**Regression modeling.** Using mixed model regression analysis with log PYY, GH AUC, cortisol AUC, and estradiol entered into the model (Table 3), log PYY and GH AUC were noted to be significant predictors of OC, log PYY was the only significant predictor of BSAP, and log PYY, GH AUC, and estradiol predicted levels of NTX/creatinine and DPD/creatinine. PICP levels were predicted by cortisol AUC and GH AUC. GH AUC was directly associated with markers of bone turnover, whereas estradiol levels correlated inversely with markers of bone resorption. Higher levels of cortisol AUC predicted lower levels of PICP. Log PYY did not predict bone density measures.

With further adjustment for BMI, log PYY remained the most significant predictor of levels of OC, BSAP, NTX/creatinine, and DPD/creatinine (accounting for 20.5, 21.4, 29.9, and 19.7 of the variability, respectively; P = 0.003, 0.003, 0.0003, and 0.007). The other significant predictor of OC and BSAP levels in this larger model was GH AUC (additional 7.9 and 5.0% of variability, respectively; P = 0.05 and 0.10). For NTX/creatinine, in addition to log PYY, significant predictors were BMI and cortisol AUC (27.0 and 5.3% of the variability; P = 0.002 and P = 0.05), and, for DPD/creatinine, the other important predictor was BMI (12.6% of the variability; P = 0.02).
effects of PYY. Obesity is associated with high levels of leptin and low levels of ghrelin (3), yet food intake is not suppressed, whereas AN is associated with low levels of leptin and high levels of ghrelin (10, 12), yet food intake is not increased.

One study examined the effects of PYY administration on glucose disposal during a hyperinsulinemic clamp in a mouse model and reported that PYY led to increased glucose disposal, an index of insulin sensitivity (35). Consistent with this report, we observed an inverse relationship between log PYY and HOMA-IR, a measure of insulin resistance.

The mechanism underlying PYY action has been examined in mice studies. Effects of PYY do not appear to be mediated via melanocortin-4 receptor signaling (16). One study determined that PYY administration resulted in a decreased food intake in fasting mice but not in freely fed mice, and, in this study, PYY administration led to a short-term suppression of NPY mRNA expression and a longer term suppression of POMC mRNA expression in the arcuate nucleus (14). However, in yet another study, POMC(+/−) mice continued to demonstrate an orexigenic effect after PYY administration (15), suggesting that PYY effects may be independent of POMC. Effects of PYY are mediated via the Y2 receptor (2), and stimulation of this receptor by PYY inhibits NPY effects through presynaptic inhibition (13). With regards to the relationship between PYY and other hormones regulating food intake, Riediger et al. (17) reported that PYY inhibits ghrelin-activated neurons of the arcuate nucleus in a dose-dependent manner. In our study, we observed a positive association between log PYY values and ghrelin AUC, and one may speculate that elevations in PYY in AN may inhibit the orexigenic effects of elevated ghrelin levels in this condition. In obese adults, PYY administration causes a decrease in ghrelin (3). In addition, we observed an inverse association between leptin and PYY in this study. However, neither leptin nor ghrelin was an independent predictor of PYY on regression modeling.

Independent predictors of PYY after multiple regression modeling in our study included nutritional markers, REE, nadir GH, and total T3, and weight recovery in 10 girls with AN was associated with a trend toward a decrease in PYY levels. The change in PYY levels with weight recovery would likely have been more significant with more weight-recovered subjects in the study. It will be important to determine whether a change in BMI predicts a change in PYY levels in a larger population of weight-recovered AN. In obese adults, similar to our data, inverse associations have been noted between PYY levels and BMI (3). Consistent with other studies (36, 37), we noted marked reductions in REE in girls with AN compared with controls, and REE was an independent predictor of PYY in our study. Because REE provides an estimate of required caloric intake, REE in chronic low-weight conditions may stimulate increased PYY secretion, which would then lead to decreased food intake commensurate with the decreased energy expenditure in that individual.

Administration of GH causes a decrease in PYY in rats (19), but, in this study, we observed a positive association between GH and PYY values. In AN, GH action, as assessed by IGF-I levels, is impaired despite high GH levels. Consistent with this, we found that IGF-I levels correlated inversely with PYY levels. In a rat study, hyperthyroidism was associated with low levels of PYY (19), and we observed an inverse association between PYY and total T3. It is uncertain, however, whether this is a direct effect of total T3 or mediated via changes in energy expenditure, or a consequence of effects of thyroid hormones on clearance of PYY. Low total T3 values in AN may merely reflect the sick euthyroid syndrome and disease severity. Of note, conditions of hyperthyroidism are associated with increased appetite. It would be interesting to monitor PYY levels in hyperthyroid patients before beginning therapy and after initiation of therapy to determine whether PYY levels decrease with treatment and whether this is associated with changes in appetite.

The inverse association of bone turnover markers with PYY values is consistent with rodent studies that demonstrate an increase in osteoblastic activity in rats with selective deletion of the Y2 receptor (20). PYY acts through the Y2 receptor, and, if Y2 receptor deletions cause activation of...
osteoosteoblasts, one may anticipate that activation of the Y2 receptor by PYY would cause a decrease in osteoblast activity. Of note, rodent studies demonstrated effects on osteoblasts alone and not on osteoclasts with Y2 receptor deletions. In our study, however, high PYY levels were associated with low values of both bone formation and resorption markers. This may reflect differences in PYY effects in humans vs. rodents or the coupling of bone formation with bone resorption. Conversely, given the correlational nature of the study, these associations may be epiphenomena. However, log PYY was a more significant predictor of bone turnover markers with regression modeling than BMI and known hormonal predictors of these markers. In keeping with known stimulatory effects of GH on bone turnover (38), GH was a positive predictor of bone turnover markers. Also, as expected given the known inhibitory effect of cortisol on bone formation (39), cortisol correlated inversely with PYY. Estradiol has known inhibitory effects on bone resorption (40), and, consistent with this, we observed inverse independent associations between estradiol and markers of bone resorption.

We thus report higher PYY levels in AN compared with healthy adolescents and a trend toward a decrease in these values with weight recovery. High PYY values independently predicted decreased fat intake, suggesting that elevated PYY levels in AN may contribute to decreased food intake and inhibit effects of elevated ghrelin levels. Of note, these data are correlational, and demonstration of increased food intake after administration of a PYY antagonist in AN would help confirm these findings. Important and independent predictors of PYY include nutritional markers, GH concentrations, and total T_4. Inverse correlations were observed between PYY and bone turnover markers, suggesting a possible role for PYY in bone metabolism. Additional studies are necessary to better understand the implications of these findings and to confirm these associations.

### Acknowledgments

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### References


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### FIG. 4. Log PYY predicted fat intake and percentage of calories from fat. Inverse correlations were observed between log PYY and fat intake, as well as percentage of calories derived from fat intake.

### TABLE 3. Predictors of bone turnover markers (mixed model stepwise regression modeling)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>F ratio</th>
<th>P value</th>
<th>Variability contributed by specific variable</th>
<th>Cumulative variability explained by model</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICP Cortisol AUC</td>
<td>7.9</td>
<td>0.009</td>
<td>15.7%</td>
<td>15.7%</td>
</tr>
<tr>
<td></td>
<td>GH AUC</td>
<td>4.2</td>
<td>0.05</td>
<td>8.1%</td>
</tr>
<tr>
<td>OC</td>
<td>Log PYY</td>
<td>12.7</td>
<td>0.003</td>
<td>20.5%</td>
</tr>
<tr>
<td></td>
<td>GH AUC</td>
<td>4.1</td>
<td>0.05</td>
<td>7.9%</td>
</tr>
<tr>
<td>BSAP Log PYY</td>
<td>10.1</td>
<td>0.003</td>
<td>21.3%</td>
<td>21.3%</td>
</tr>
<tr>
<td>NTX/creatinine Log PYY</td>
<td>31.4</td>
<td>0.0003</td>
<td>29.9%</td>
<td>29.9%</td>
</tr>
<tr>
<td></td>
<td>GH AUC</td>
<td>12.2</td>
<td>0.01</td>
<td>11.3%</td>
</tr>
<tr>
<td>Estradiol DPD/creatinine</td>
<td>7.3</td>
<td>0.01</td>
<td>10.0%</td>
<td>51.2%</td>
</tr>
<tr>
<td></td>
<td>Log PYY</td>
<td>21.1</td>
<td>0.001</td>
<td>27.0%</td>
</tr>
<tr>
<td></td>
<td>GH AUC</td>
<td>6.3</td>
<td>0.07</td>
<td>7.0%</td>
</tr>
<tr>
<td>Estradiol</td>
<td>4.7</td>
<td>0.04</td>
<td>8.3%</td>
<td>42.2%</td>
</tr>
</tbody>
</table>