Changes in Bone Turnover in Patients with Anorexia Nervosa during Eleven Weeks of Inpatient Dietary Treatment

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Background: Many adolescents with anorexia nervosa suffer from severe osteopenia and osteoporosis. We hypothesized that individualized nutrition therapy may improve bone turnover in anorectic patients.

Methods: We studied 19 female patients [mean age, 14.2 ± 1.4 years; mean body weight, 39.3 ± 5.4 kg; mean body mass index (BMI), 14.2 ± 1.4 kg/m²] with anorexia nervosa (International Classification of Diseases-10: F50.0, F50.1) for a period of 3 months. Nutrition therapy began at the end of the first week and included individualized hypercaloric diets, high calcium intake (2000 mg/day), and administration of vitamin D (400 IU/day). Blood samples were taken at baseline and again in weeks 3, 7, and 11. We measured serum calcium, parathyroid hormone, bone formation and resorption markers, insulin-like growth factor 1 (IGF-1), and leptin.

Results: Mean BMI increased significantly, from 14.2 ± 1.4 to 17.1 ± 0.7 kg/m² (P < 0.000001), during the course of treatment, whereas serum total calcium and phosphate concentrations remained unchanged. The bone formation markers procollagen-I carboxy-terminal propeptide and bone alkaline phosphatase almost doubled (P = 0.006). Both IGF-1 (P = 0.00001) and leptin (P = 0.000005) increased significantly by week 11. Parallel to this, the serum concentration of C-telopeptide, a bone resorption marker, decreased significantly (P = 0.009).

Conclusions: Nutritional rehabilitation, possibly as a result of increasing IGF-1 and leptin concentrations, may increase bone formation. It therefore provides additional objective evidence of the importance of nutrition for bone.

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Anorexia nervosa is defined either as a weight loss of 15% or more of that expected for age and height (Diagnostic and Statistical Manual of Mental Disorders IV) or as a Quetelet's body mass index (BMI) < 17.5 kg/m² (International Classification of Diseases-10). The lifetime prevalence among women, with an increasing incidence in women 15–24 year of age, is reported as 0.5–3.7% (1–7). In at least 5% of patients, anorexia has a prepubertal onset (8, 9). The restricted eating pattern is associated with profound metabolic complications, including prolonged amenorrhea, growth hormone resistance, increased plasma cortisol, low production of insulin-like growth factor 1 (IGF-1) (10, 11), and decreased leptin concentrations (12, 13). Long-term studies of up to 10 years have demonstrated that in the majority of patients, anorexia nervosa takes a protracted course with recurrent periods of relapse (14, 15).

One of the most important long-term somatic complications of anorexia nervosa is the decrease in bone mineral density, which leads to spontaneous fractures (16, 17). The mechanisms that trigger bone loss in these patients is not fully understood. In >50% of female patients, anorexia nervosa is associated with osteopenia (2, 5, 18, 19). Anorectic patients have a sevenfold in-

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The results of this study are part of a doctoral thesis by C. Mika.

Received October 19, 2001; accepted February 20, 2002.

Nonstandard abbreviations: BMI, body mass index; IGF-1, insulin-like growth factor 1; BMD, bone mineral density; BCM, body cell mass; PTH, parathyroid hormone; DHEAS, dehydroepiandrosterone sulfate; PICP, procollagen-I carboxy-terminal propeptide; bAP, bone alkaline phosphatase; and sCTX, serum C-terminal telopeptide.
creased incidence of spontaneous fractures, which occur at multiple sites (16). In 85% of anorexia nervosa patients who are considered partially recovered and who have also resumed menses and attained weight rehabilitation to within 10% of ideal body weight, deficient bone mineral density (BMD) persists (20).

Adolescence is a critical time in bone metabolism because most of the peak bone mass is accumulated during these years (21). Hence, deficient nutrient intake together with reduced serum concentrations of pubertal hormones, such as 17β-estradiol, IGF-1, and leptin, may retard relevant bone growth and development. Starvation is accompanied by high serum cortisol, which enhances bone resorption (10). Estrogen is an important hormone for bone mineralization (22). Although in postmenopausal women the administration of oral estrogen has been shown to be successful in counteracting decreases in BMD (23), it seems ineffective in anorexia nervosa patients (19,24–28). Insufficient alimentary calcium and vitamin D consumption increases bone resorption (29) and prevents the formation of peak bone mass (21,30). High calcium intake and vitamin D supplementation in healthy adolescent females lead to an increase in BMD (31–34). Furthermore, daily supplementation with 1500 mg of calcium and 800 IU of vitamin D has been shown to stabilize BMD in patients with corticosteroid-induced osteoporosis (35). Weight gain reverses bone turnover in patients with anorexia nervosa (36). However, the chronology of the bone remodeling events after refeeding is still unclear (36).

We tested the hypothesis that nutritional therapy would improve bone turnover as reflected by markers of bone turnover.

**Materials and Methods**

**Patients**

Nineteen female adolescent inpatients (mean age, 14.2 ± 1.4 years; range, 11.5–17.4 years; mean body weight, 39.3 ± 5.4 kg; range, 27.4–47.3 kg; mean BMI, 14.2 ± 1.4 kg/m²; range, 11.4–17.4 kg/m²) diagnosed as having anorexia nervosa (International Classification of Diseases-10: F50.0, F50.1) participated in the study. The mean duration of the disease was 11.4 ± 1.6 months (range, 3–27 months) before admission to the Department of Child and Adolescent Psychiatry and Psychotherapy of the Technical University of Aachen. Thirteen patients had secondary amenorrhea for more than 6 months. Six patients had never menstruated.

**Study Design**

The investigation took place at the Department of Child and Adolescent Psychiatry and Psychotherapy of the Technical University of Aachen, Germany. The study was approved by the ethics committee of the University of Aachen and was in accordance with the current revision of the Helsinki Declaration. All patients and their parents gave written informed consent.

The patients were studied immediately after admission and in weeks 3, 7, and 11 of treatment. At each point, body weight and BMI were determined. Lean body mass, body cell mass (BCM), and fat mass analysis were determined by body impedance analysis. Morning blood (0800) was drawn, with patients in a fasting state, for routine laboratory analyses, including serum calcium and phosphates, and for parathyroid hormone (PTH), 17β-estradiol, progesterone, dehydroepiandrosterone sulfate (DHEAS), cortisol, procollagen-I carboxy-terminal propeptide (PICP), bone alkaline phosphatase (bAP), IGF-1, serum C-terminal telopeptide (sCTX), and leptin concentrations. During inpatient treatment, the patients were physically active, but were not allowed to engage in excessive exercise. During the first week, the patients were allowed an activity level equivalent to a light physical workload. After 6–8 weeks in hospital, their activity level was comparable to medium muscular workload.

During treatment patients did not vomit or use laxatives. None of them received hormone replacement therapy during the study.

**Diet**

After a short observation period of 2–3 days, the patients received an appropriate, individualized diet containing 7.8 ± 0.6 MJ/day for week 1. The caloric intake was increased continuously to 9.3 ± 0.7 MJ/day during week 11. Dietary protein, fat, and carbohydrate intake was calculated according to dietary reference intake values (37), i.e., 15–20% of the daily energy intake was protein, 30% was fat, and 50–55% was carbohydrates. Immediately after admission, most of the patients (18 of 19) had to be fed by gastrointestinal tube, but after a few days, they were able to ingest solids. At the beginning of the second week, we increased the dietary calcium intake to 2000 mg/day by adding Calcium Sandoz forte® to the diet. Adolescent patients with anorexia nervosa often have reduced 25-OH-vitamin D concentrations (38). To compensate for any change in vitamin D concentrations, we administered 400 IU of ergocalciferol daily in a multivitamin tablet (Osspubvit® S forte) containing 400 IU of ergocalciferol (vitamin D₂), 5000 IU of retinol acetate (vitamin A), 10 mg of α-tocopherol (vitamin E), 5 mg of thiamin (vitamin B₁), 5 mg of riboflavin (vitamin B₂), 0.5 mg of pyridoxine hydrochloride (vitamin B₆), 50 mg of ascorbic acid (vitamin C), 15 mg of nicotinamide, and 493 mg of calcium hydrogen phosphate. The calcium from the multivitamin capsule was included in the 2000-mg daily calcium intake.

**Blood Samples**

Blood samples were taken by a short catheter in serum monovettes (Sarstedt) from the antecubital vein. Immediately thereafter the monovettes were divided into two parts. One part was immediately taken to the laboratory for centrifugation and the analysis of serum calcium, 17β-estradiol, DHEAS, and progesterone. Total serum
Calcium was determined by the o-cresolphthalein method (Hitachi 747). Automated chemiluminescence systems (Centaur®; Chiron Diagnostics) were used to analyze 17β-estradiol (Centaur Estradiol 6; cat. no. 110785), and progesterone (Centaur progesterone; cat. no. 118530). DHEAS was analyzed by a competitive immunoassay on the IMMULITE® Analyzer (DPC®). To guarantee the validity of the data, the laboratory routinely takes part in independent control analysis of these analytes.

The second part of each monovette was centrifuged immediately. Serum was distributed into small tubes and immediately frozen at −40 °C until analysis. Serum phosphate concentrations were analyzed by the molybdate method (Hitachi 747). Commercially available RIAs were used to analyze PTH (PThiact; Nichols Institute Diagnostics), bAP (Tandem® R Ostase; Hybritech), PICP (Oriion Diagnostica), IGF-1 (Nichols Institute Diagnostics), sCTX (Crosslaps®; IBL), and leptin (Human-Leptin-RIA sensitiv; Mediagnost). Each patient’s serum was analyzed in duplicate or triplicate in one assay to avoid interassay variation.

Body Composition
At the time of admission and during weeks 3, 7, and 11, BMI was calculated, using the equation: BMI = body weight (kg) divided by squared body length (m²). During weeks 3, 7 and 11, lean body mass, BCM as an indicator of nutritional status, and fat mass were determined in 18 of the 19 patients by a body impedance analysis device (BIA 2000-M with Nutri 4 software; Data Input). Two electrodes were placed on the right hand and two on the right foot. Four frequencies (100, 50, 5, and 1 kHz) were measured to analyze lean body and fat masses. The respective calculations were performed using the commercially available software Nutri 4, provided by the manufacturer (Data Input).

Statistical Analysis
The data are presented as the mean ± SD. Statistical analyses were performed with the statistical analysis software SYSTAT 10.0 (39). To test the effect of nutritional rehabilitation during the examination period, we used repeated-measures ANOVA to compare data from baseline and weeks 3, 7, and 11. Significant differences between the relevant examinations were tested by the F-test. Because baseline data were lacking for lean body and fat mass, data from weeks 3, 7, and 11 were used for the ANOVA testing. The Pearson correlation coefficient was calculated for the following variables: leptin vs BMI, leptin vs fat mass, PICP vs leptin, bAP vs leptin, and sCTX vs leptin. P < 0.05 was considered the minimum level of significance.

Results
The concentrations of serum calcium, phosphate, PTH, cortisol, 17β-estradiol, and progesterone are shown in Table 1. At baseline, serum calcium was 2.52 ± 0.14 mmol/L, which was within the reference interval (reference interval for adults, 2.1–2.6 mmol/L). In week 11 of dietary treatment, serum calcium was 2.46 ± 0.10 mmol/L, indicating no change (repeated-measures ANOVA, P = 0.530). Serum phosphate did not change during the 11 weeks of treatment (P = 0.527).

Mean serum PTH was 21.12 ± 10.57 ng/L on admission. At the end of week 11 of treatment, serum PTH was significantly increased compared with baseline, to 27.43 ± 13.05 ng/L (repeated-measures ANOVA, P = 0.0078). When we compared the relevant examination periods, the increase between week 7 and week 11 was significant (P = 0.021).

Mean serum DHEAS was 4.48 ± 2.78 μmol/L at baseline. The DHEAS concentration did not change in the course of treatment when evaluated by repeated-measures ANOVA (P = 0.560).

On admission, the mean serum cortisol concentration was 655.42 ± 261.07 nmol/L, more than 25% higher than the upper limit of the reference interval for female adolescents up to the age of 16 years (reference interval, 118–413 nmol/L). At the end of the week 11 of treatment, the mean cortisol concentration was almost the same, at 552.28 ± 122.71 nmol/L (Table 1; repeated-measures ANOVA, P = 0.317).

At baseline, serum 17β-estradiol (52.53 ± 32.39 pmol/L) was within the reference values for prepubescent children (<130 pmol/L). In the course of treatment, the 17β-estradiol concentration increased significantly (105.17 ± 92.11 pmol/L; repeated-measures ANOVA, P = 0.0038; Table 1), but this was still within the reference

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Table 1. Mean values of 19 patients with anorexia nervosa in the course of dietary treatment.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 3</th>
<th>Week 7</th>
<th>Week 11</th>
<th>P, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium, mmol/L</td>
<td>2.52 ± 0.14</td>
<td>2.48 ± 0.11</td>
<td>2.46 ± 0.10</td>
<td>2.46 ± 0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Serum phosphate, mmol/L</td>
<td>1.32 ± 0.17</td>
<td>1.36 ± 0.15</td>
<td>1.36 ± 0.11</td>
<td>1.33 ± 0.12</td>
<td>NS</td>
</tr>
<tr>
<td>PTH, ng/L</td>
<td>21.12 ± 10.57</td>
<td>18.87 ± 7.41</td>
<td>19.29 ± 8.00</td>
<td>27.43 ± 13.05</td>
<td>0.0078</td>
</tr>
<tr>
<td>Cortisol, nmol/L</td>
<td>655.42 ± 261.07</td>
<td>585.05 ± 201.52</td>
<td>602.42 ± 158.97</td>
<td>552.28 ± 122.71</td>
<td>NS</td>
</tr>
<tr>
<td>17β-Estradiol, pmol/L</td>
<td>52.52 ± 32.40</td>
<td>64.11 ± 44.17</td>
<td>67.84 ± 56.13</td>
<td>105.17 ± 92.11</td>
<td>0.0038</td>
</tr>
<tr>
<td>DHEAS, μmol/L</td>
<td>4.48 ± 2.78</td>
<td>4.02 ± 2.24</td>
<td>4.16 ± 3.26</td>
<td>4.05 ± 2.56</td>
<td>NS</td>
</tr>
<tr>
<td>Progesterone, nmol/L</td>
<td>2.17 ± 1.01</td>
<td>2.09 ± 1.20</td>
<td>1.97 ± 1.21</td>
<td>1.81 ± 0.79</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Statistical analysis was by repeated-measures ANOVA. Values are the mean ± SD.

NS, not significant.
values for prepubescent children (<130 pmol/L). Further evaluation of the relevant examination periods revealed that the main increase in 17β-estradiol tended to take place between week 7 and week 11 (P = 0.058). However, 16 of the 19 patients were still amenorrheic at the end of the observation period.

Serum progesterone was analyzed in 17 of the 19 patients. The mean concentration on admission was 2.17 ± 1.01 nmol/L and did not change in the course of treatment when evaluated by repeated-measures ANOVA (P = 0.358; Table 1).

The changes in the leptin and IGF-1 concentrations in the anorexia nervosa patients are shown in Fig. 1. At baseline, serum leptin (1.91 ± 1.16 μg/L) was lower than the values for comparable healthy individuals (values for healthy individuals at Tanner 3 and 4, 2–10 μg/L). During the nutritional rehabilitation, leptin increased significantly (repeated-measures ANOVA, P = 0.000002). When we further analyzed the leptin concentrations of the relevant periods, we could see a significant increase in leptin were obvious from week 3 to week 7 and from week 3 (P = 0.0055). Additional significant increases in leptin were observed from week 3 to week 7 and from week 7 to week 11 (week 7, P = 0.00002; week 11, P = 0.026).

The mean serum IGF-1 concentration was 206.74 ± 75.48 μg/L on admission. In the course of treatment, serum IGF-1 increased significantly (repeated-measures ANOVA, P = 0.000000001). Post hoc testing showed that the IGF-1 concentration increased mainly between week 3 and week 7 (P = 0.000076) and the following period, week 7 to week 11 (P = 0.04).

At baseline, the mean BMI was 14.2 ± 1.4 kg/m². By week 11, the BMI had increased significantly, to 17.06 ± 0.68 kg/m² (repeated-measures ANOVA, P = 0.1 × 10⁻¹⁴). The BMI increased significantly during the first examination period of 2 weeks (P = 0.000002), and it continued to increase significantly in the following two examination periods (week 3 to week 7, P = 0.12 × 10⁻¹⁰; week 7 to week 11, P = 0.00005). Lean body mass at week 3 could be measured in only 15 of the 19 patients. In this group, lean body mass was 36.9 ± 3.6 kg. During the treatment period, lean body mass increased significantly, to 37.8 ± 2.9 kg (repeated-measures ANOVA, P = 0.008). Lean body mass increased from week 3 to week 7 (P = 0.0025) as well as in the following examination period (P = 0.10). BCM as part of lean body mass also increased significantly, from 16.4 ± 1.4 kg in week 3 to 18.1 ± 1.4 kg during the treatment (repeated-measures ANOVA, P = 0.046), which was slightly below the minimum for the optimal range (18.7 ± 2.2 kg). However, when we compared the data from week 3 to week 7 or from week 7 to week 11, we found no significant change, only a trend of increasing BCM from week 7 to week 11 (week 7, 16.9 ± 1.3 kg; week 11, 18.1 ± 1.4 kg; P = 0.075). The average fat mass of the 15 patients in week 3 was 5.7 ± 2.7 kg and increased significantly during the 11 weeks of treatment (9.6 ± 2.3 kg; repeated-measures ANOVA, P = 0.694 × 10⁻⁷). Thus, fat mass increased continuously starting in the first examination period (week 3 to week 7, P = 0.0000028) until the end of the study (week 7 to week 11, P = 0.0013).

The changes in the bone formation markers PICP and bAP are shown in Fig. 2, A and B, respectively. At baseline, the serum PICP concentration was 129.89 ± 40.59 μg/L. During the nutrition treatment, serum PICP increased significantly, to 234.55 ± 123.31 μg/L (repeated-measures ANOVA, P = 0.0000034). Thus, PICP did not increase in the first 2 weeks, but from week 3 to week 7, PICP increased significantly (P = 0.018) and continued to increase in the next examination period, week 7 to week 11 (P = 0.010; Fig. 2A). The same time course held true for serum bAP, which increased significantly from 16.01 ±

Fig. 1. IGF-1 (A) and leptin (B) concentrations in 19 adolescent patients with anorexia nervosa during 11 weeks of dietary treatment.

The diet consisted of individualized hypercaloric nutrition, 2000 mg of calcium/day, and 400 IU of vitamin D/day. Values are the mean value ± SD (bars). *, P < 0.05; **, P < 0.01; ***, P < 0.001; NS, not significant.
9.70 \mu g/L at the time of admission to 24.51 \pm 15.34 \mu g/L in week 11 of treatment (repeated-measures ANOVA, \( P = 0.0001 \)). Thus, bAP increased significantly from week 3 to week 7 (\( P = 0.00015 \)) and during the next examination period (week 7 to week 11, \( P = 0.026 \); Fig. 2B).

The changes in the bone resorption marker sCTX are shown in Fig. 3. At baseline, sCTX concentration was 10 496.6 \pm 4567.78 pmol/L. By week 11 of treatment, sCTX had decreased significantly (repeated-measures ANOVA, \( P = 0.00019 \)) to 7560.8 \pm 3349.43 pmol/L. The kinetics of the decrease in sCTX were as follows. sCTX decreased significantly between baseline and week 3 (\( P = 0.010 \)) and between week 3 and week 7 (\( P = 0.017 \)). Between week 7 and week 11, there were no additional decreases in sCTX.

Calculating the Pearson correlation coefficient from baseline to week 11 revealed a good correlation between leptin and BMI (\( r = 0.529; P = 0.00000088 \)), between PICP and leptin (\( r = 0.463; P = 0.0026 \)), and between bAP and leptin (\( r = 0.480; P = 0.000011 \)). The correlation coefficient between leptin and fat mass (only week 3 to week 11) was \( r = 0.323 \) (\( P = 0.025 \)). We found no correlation between sCTX and leptin (\( r = -0.215; P = 0.061 \)).

**Discussion**

To the best of our knowledge, we are the first to show the kinetics of increasing bone formation and decreasing bone resorption in young anorectic adolescents (range, 11.5–17.4 years) after nutritional rehabilitation. Bone formation increased significantly, as shown by the formation markers IGF-1, PICP, and bAP, as a result of the nutrition therapy. Together with the fact that leptin concentrations increased more than threefold in week 11 of nutrition therapy, these data show that nutritional rehabilitation can have beneficial effects on bone turnover in adolescent patients with anorexia nervosa.

Serum IGF-1 is reduced in anorexia nervosa patients and is regarded as a predictor for the recovery of bone mass in this disease (27). Our adolescent patients showed 50% lower serum IGF-1 concentrations than healthy individuals of the same age, which is consistent with data on
adult patients with anorexia nervosa published by Argente et al (40). However, in our study the dietary regimen, most probably the high caloric intake, induced IGF-1 secretion. Thus, the first 2 weeks of diet therapy did not produce a significant increase in IGF-1. IGF-1 began increasing significantly in week 3, with a continuous increase of 50% up to week 11, suggesting a delayed reaction to nutritional rehabilitation. In a very short-term study by Grinspoon et al. (12), the administration of 30 μg of IGF-1/kg of body weight for 6 days was associated with a significant increase in PICP in young women with anorexia nervosa without any effect on bone resorption. However, the dietary regimen in our patients induced an increase in bone formation, as shown by increased PICP and bAP together with an initial decrease in bone resorption.

Leptin and its receptor are important for regulating food intake and energy metabolism. Thus, the increase in leptin to 315% of the original value in week 11 together with the restoration of fat tissue, as described by other authors (13), was expected. The kinetics of increasing leptin concentration during diet therapy were similar to those of IGF-1. Although leptin increased significantly, by 28%, from baseline to week 3, the most pronounced increase of 91% took place from week 3 to week 7, suggesting that during nutrition therapy some time is necessary to activate adipocytes to synthesize leptin. When we compared the increase in leptin with that in fat mass, the increases in leptin concentration exceeded the increase in fat mass. Although leptin increased by 315% up to the end of treatment, fat mass increased only slightly, by 16%. The strong correlation between leptin and the bone formation markers might suggest a cause-and-effect relationship between leptin concentrations and the bone formation process, as has already been stressed by others (41).

Bone resorption was assessed by sCTX, which has been a valid biomarker (42). During the 11 weeks of treatment, the bone formation markers increased, whereas bone resorption decreased. However, when we looked at the kinetics of the markers, the process of change in bone formation and resorption was not continuous. During the first study phase of 2 weeks, the two bone formation markers, PICP and bAP, remained constant. In contrast, the CTX concentration decreased significantly by 13%. In the second study phase of 4 weeks (from week 3 to week 7), PICP continued to increase significantly, whereas CTX showed further decreases. In the last 4-week study phase (from week 7 to week 11), however, the bone formation markers continued to increase (PICP by 35%; bAP by 36%) compared with the second study phase, whereas CTX stayed constant. We also found a dissociation of bone turnover at baseline (low bone formation and high bone resorption) in most of our patients compared with healthy adolescents, which is consistent with earlier reports (36). However, nutrition therapy stimulated the bone formation process after week 3 and suppressed bone resorption until week 7. One may speculate whether dietary therapy may restore the coupling of bone turnover after 11 weeks.

The strikingly low BMI of 14 kg/m² in our cohort indicates the severity of the disease. The chosen dietary regimen, which was integrated with intensive psychiatric treatment, induced a BMI increase of ~20% until the end of our examination. According to our analyzed multifrequency impedance data, this increase was mainly attributable to an increase in fat mass, an increase in BCM, and a decrease in extracellular volume.

It is well known that hypophosphatemia often occurs in patients with anorexia nervosa during parenteral refeeding (43) or starvation (44). A clinical consequence of low phosphate is, among others, osteomalacia. This is the result of increased bone resorption to correct low serum phosphate (44). In our cohort, however, serum calcium and phosphate concentrations were within the appropriate reference intervals and did not decrease after the dietary treatment. Changes in phosphate concentrations can therefore not explain the positive effect of the diet on bone turnover.

Although consistent results were obtained in our patients, the conclusion is limited by the small sample size of 19 patients. In addition, the study focused more on nutritional rehabilitation than the evaluation of single nutrients on bone metabolism. Further studies are thus needed to demonstrate the cause-and-effect relationship of single nutrients on bone metabolism in patients with malnutrition, such as anorexia nervosa, compared with controls. Our findings also warrant replication in a larger sample of patients and could include the exact monitoring of physical activity and the effects of age and pubertal state.

We are very grateful to the patients who participated in this study. We acknowledge Novartis GmbH (Munich, Germany), who sponsored the Calcium Sandoz forte for the patients. We also wish to thank N. Heussen, Institute of Biometrics, RWTH Aachen for statistical advice. The study was supported by the START program of the Technical University of Aachen (Aachen, Germany) and by the Directorate ’Raumfahrt’ of the German Aerospace Center (Cologne, Germany).

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