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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Bone Mineral Density Improvement After Lung Volume Reduction Surgery for Severe Emphysema*

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Background: In patients with severe emphysema, bone mineral density (BMD) is reduced and the risk of osteoporosis is increased.

Study objectives: To identify the impact of lung volume reduction surgery on BMD.

Design: Prospective cohort study.

Setting: University hospital.

Patients and interventions: Forty emphysematous patients, all receiving oral steroid therapy, underwent bilateral lung volume reduction surgery. Thirty similar patients, who refused the operation, followed a standard respiratory rehabilitation program.

Measurements: All subjects were evaluated pretreatment and 12 months posttreatment for respiratory function, nutritional status, and bone-related biochemical parameters. BMD was assessed by dual-energy radiograph absorptiometry.

Results: After surgery, we observed significant improvements in respiratory function (FEV₁, +18.8% [p < 0.01]; residual volume [RV], -29.6% [p < 0.001]; diffusing capacity of the lung for carbon monoxide [DLCO], +21.6% [p < 0.01]) nutritional parameters (fat-free mass, +6.0% [p < 0.01]), levels of bone-related hormones (free-testosterone, +20.5% [p < 0.01]; parathormone, -11.2% [p < 0.01]), bone turnover markers (osteocalcin, -12.7% [p < 0.05]; bone-alkaline-phosphatase, -14.0% [p < 0.05]; β -crosslaps, -33.6% [p < 0.001]), BMD (lumbar, +8.8% [p < 0.01]; femoral, +5.5% [p < 0.01]), and T-score (lumbar, +21.0% [p < 0.01]; femoral, +12.4% [p < 0.01]) with reduction in osteoporosis rate (50 to 25%). Nineteen patients who had undergone surgery were able to discontinue treatment with oral steroids. These subjects showed a more significant improvement in BMD (lumbar, +9.6%; femoral, +6.8%; p < 0.001) and T-score (lumbar, +27.3%; femoral, +14.3%; p < 0.001). The remaining 21 patients who had undergone surgery experienced significant improvement compared to respiratory rehabilitation subjects despite continued therapy with oral steroids (BMD: lumbar, +4.5% vs -0.7%, respectively [p < 0.01]; femoral, +2.7% vs -1.1%, respectively [p < 0.05]; T-score: lumbar, +14 vs -2.1, respectively [p < 0.01]; femoral, +7.4 vs -2.7, respectively [p < 0.01]). The increase in lumbar BMD was correlated with the surgical reduction of RV (p = 0.02) and with the increase in DLCO (p = 0.01) and fat-free mass (p = 0.01).

Conclusions: Lung volume reduction surgery significantly improves BMD compared to respiratory rehabilitation therapy, even in patients requiring oral steroids. The increase in BMD correlates with RV, DLCO, and fat-free mass, suggesting that the restoration of respiratory dynamics, gas exchange, and nutritional status induces improvement in bone metabolism and mineral content. (CHEST 2005; 127:1960-1966)

Key words: COPD; lung volume reduction surgery; osteoporosis; respiratory rehabilitation

Abbreviations: BMD = bone mineral density; DLCO = diffusing capacity of the lung for carbon monoxide; IQR = interquartile range; RV = residual volume

COPD produces significant systemic biochemical and clinical alterations.¹ In patients with severe emphysema, persistent elevation of inflammatory mediators, chronic hypoxia, and impaired respiratory dynamics lead to a hypermetabolic-catabolic condition^{2,3} with progressive cachexia. Weight loss occurs largely due to a loss of fat-free mass.⁴⁻⁶ Bone mineral density (BMD) declines,⁷ leading to a higher incidence of vertebral and femoral fractures.^{8,9} The

osteoporosis associated with emphysema is multifactorial, and is due in part to the respiratory disease itself, in part to steroid therapy,^{10,11} and in part to additional factors such as secondary endocrine abnormalities,¹² aging, inactivity, low caloric intake, smoking, and vasculopathy.¹³

Lung volume reduction surgery has been shown to be effective in improving respiratory function and quality of life in properly selected emphysematous

patients,¹⁴ compared to medical and respiratory rehabilitation therapy.^{15,16} Little information is available about changes in bone mineral content after

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lung volume reduction surgery. We hypothesized that surgical therapy may improve not only respiratory function and nutritional status, but also metabolism and bone mass.

The aim of this study was to analyze the impact of lung volume reduction surgery on BMD. Correlations among respiratory, nutritional, and bone-related parameters were evaluated in order to delineate the mechanisms involved in any observed changes.

MATERIALS AND METHODS

The trial was designed as a prospective nonrandomized study by evaluating the effects of surgery and respiratory rehabilitation therapy on patients with severe emphysema. The analysis included intragroup evaluations (*ie*, from baseline to 12 months posttreatment) and intergroup evaluations (*ie*, surgery vs respiratory rehabilitation). The study was approved by the ethical committee of our institution and was activated in July 1999. Patients were recruited until December 2002. Written informed consent was obtained from all patients.

Indications for lung volume reduction surgery have been previously reported.¹⁷ The study inclusion criteria required the patients to be clinically stable, performing regular mild physical activity, and receiving an adequate and balanced diet, with an appropriate intake of calcium and vitamin D₃. Patients receiving long-term oxygen therapy who had a history of recurrent fractures, concomitant diseases, or long-term therapy that was capable of interfering with bone metabolism and mineral density were excluded from the study. Patients were considered for analysis only if they continued to fulfill these criteria throughout the entire follow-up period.

Seventy male patients with heterogeneous, symmetric, and mainly upper lobe-located emphysema apparent on high-resolution CT scan and/or perfusion scan, were selected for lung volume reduction surgery. Forty patients (median age, 61.0 years;

interquartile range [IQR], 56 to 69) underwent one-stage bilateral reduction through four-port videothoroscopic accesses. The most damaged portions of the lung were reevaluated by direct intraoperative inspection and resected using simple non-protected suture lines, if possible excising a single strip of parenchyma in order to reduce about 30% of the lung volume. To facilitate lung reexpansion, the pulmonary ligament was routinely divided. Neither pleural abrasion nor tent protection was performed.

The remaining 30 selected patients (median age, 60.5 years; IQR, 58 to 69 years) refused surgery for personal reasons (*eg*, psychological rejection of a surgical procedure, fear of postoperative complications, or lack of confidence in surgery) and were included in a standard respiratory rehabilitation program¹⁶ twice during the year.

At the time of the initial assessment, all patients were receiving therapy with oral and inhaled steroids and inhaled β_2 -agonists. During the year preceding and following the treatment, the median daily dosage was calculated using the values collected every 3 months by our medical surveillance center. Respiratory assessments included timed spirometry, plethysmography, single-breath measurement of the diffusing capacity of the lung for carbon monoxide (DLCO), and arterial blood gas analysis.

Exercise tolerance was assessed with a standard 6-min walking test. Dyspnea was rated according to the Medical Research Council score of the American Thoracic Society.¹⁷ Quality of life was assessed with the St. George Respiratory Questionnaire¹⁸ using the general score domain (best score, 0; worst score, 100).

Anthropometrics and biochemical and bone-related hormone measurements were made. Serum markers of bone turnover included bone-specific alkaline phosphatase, osteocalcin, and β -crosslaps (*ie*, cross-linked C-terminal telopeptide of type I collagen). BMD and body composition were measured by dual-energy radiograph absorptiometry (DEXA) using a total body scanner (model QDR 2000; Hologic; Waltham, MA), with a radiograph source, an internal wheel to calibrate the bone mineral component, and an external methyl methacrylate polymer (Lucite; Lucite International; Southampton, UK) and aluminum phantom to determine the fat percentage of each scanned soft-tissue sample.¹⁹ Calibration was performed daily. Measurements were calculated using matched, referenced population data and a computer algorithm provided by the manufacturer. Coefficients of variability were < 1% and 1.5%, respectively, for BMD and body composition.

Individual measurements of the anterior-posterior lumbar spine (L2-L4), left hip (femoral neck), and total body BMD were expressed in absolute values and relative T-scores. This score represents the difference in SDs from mean reference BMD values that have been matched for race and sex from peak bone mass.²⁰ Fat-free mass was also determined.

All measurements were performed at baseline and 12 months posttreatment. This time frame was chosen as the appropriate period in which to expect the maximum improvement in both respiratory and bone-related parameters.

Descriptive statistics were presented as the median and IQR, while posttreatment changes were indicated as the median percentage of the baseline value. Due to the nonnormal distribution of some variables and the small sample size, nonparametric tests for paired and unpaired comparison (Wilcoxon rank sum test and Mann-Whitney test, respectively) were used, the latter using the 12-month percentage change values for analysis.

To evaluate the impact of oral steroid therapy on bone metabolism, we analyzed the patients who had undergone surgery who were able to discontinue therapy with oral steroids, and those who had undergone surgery who continued with therapy. This last subset of patients was also compared with the respiratory rehabilitation group. In the surgical group, correlations

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among respiratory, nutritional, and bone-related parameters were evaluated using 12-month postoperative percentage changes (Spearman test).

RESULTS

Intragroup Evaluation

All patients in both groups were available for a 12-month follow-up. After surgery, significant improvements were found in the majority of respiratory, symptomatic, and nutritional parameters (Table 1). Body mass index (+5.6%; $p < 0.01$) and fat-free mass (+6.0%; $p < 0.01$) significantly increased. Bone-related hormones significantly changed, as follows: free-testosterone, +20.5% ($p < 0.01$); and

parathormone (−11.2%; $p < 0.01$). The levels of bone turnover markers decreased, with the relative prevalence of a bone resorption phase (β -crosslaps, −33.6%; $p < 0.001$) over the deposition phase (osteocalcin, −12.7% [$p < 0.05$]; bone alkaline phosphatase, −14.0% [$p < 0.05$]). BMD significantly increased, mainly in lumbar districts (+8.8%; $p < 0.01$), but also in femoral districts (+5.5%; $p < 0.01$) and total body districts (+4.1%; $p < 0.05$). The relative T-scores showed a consequent improvement (lumbar, +21.0% [$p < 0.01$]; femoral, +12.4% [$p < 0.01$]; total body, +7.4% [$p < 0.05$]), resulting in a cumulative postoperative reduction of the osteoporosis rate (50 to 25%) and in a relative shift to osteopenia (35 to 50%).

Table 1—Patients Selected for Lung Volume Reduction Surgery and Respiratory Rehabilitation: Intragroup and Intergroup Comparison of 12-Month Changes*

Measurements	LVRS (n = 40)		RR (n = 30)		Intergroup p Value
	Baseline	Change, %	Baseline	Change, %	
FEV ₁ , L	1.04 (0.9–1.6)	18.8†	1.08 (0.9–1.3)	7.4‡	< 0.001
RV by plethysmography, L	5.6 (5.1–6.4)	−29.6§	5.5 (4.7–5.9)	0.4	< 0.0001
DLCO, mmol/KPa/min	3.9 (2.4–4.5)	21.6†	3.8 (2.9–4.3)	0.3	< 0.001
PaO ₂ , KPa	9.3 (8.5–10.6)	9.7†	9.1 (8.5–9.7)	4.9‡	< 0.01
PaCO ₂ , KPa	5.1 (4.1–5.6)	2.3	5.1 (4.3–5.8)	3.6	NS
Dyspnea index	2.5 (2.0–3.0)	−58.3§	3.0 (3.0–4.0)	−33.3†	< 0.001
SGRQ general score (score 0–100)	22.1 (13.4–27.8)	−20.6†	21.2 (10.1–33.9)	−7.8‡	< 0.001
6-min walking test, m	400 (300–455)	10.4†	405 (380–427)	5.1‡	< 0.01
Body mass index, Kg/m ²	22.9 (20.7–25.0)	5.6†	23.0 (21.8–24.4)	−1.3	< 0.01
Fat-free mass, Kg	48.6 (44.1–53.1)	6.0†	50.7 (46.2–53.2)	−2.8	< 0.001
Total protein, g/dL	7.1 (6.7–7.5)	10.5‡	7.0 (6.1–7.4)	0.6	< 0.01
Albumin, g/dL	4.0 (3.1–4.2)	15.7†	4.1 (3.5–4.2)	0.2	< 0.001
Transferrin, mg/dL	221 (211–312)	14.1‡	225 (206–319)	0.5	< 0.01
Total cholesterol, mg/dL	154 (102–212)	11.9†	151 (123–179)	−4.6	< 0.001
Calcium, mg/dL	10.0 (9.9–10.4)	−0.3	10.1 (9.8–10.5)	0.9	NS
Phosphate, mg/dL	3.30 (3.1–3.4)	0.2	3.1 (3.1–3.5)	0.1	NS
Luteinizing hormone, mUI/mL	4.3 (3.7–9.6)	6.1	4.1 (3.8–9.2)	2.2	NS
Free testosterone, pg/mL	5.5 (2.0–8.3)	20.5†	5.3 (2.2–7.5)	0.1	< 0.001
β -17 estradiol, pg/mL	23.0 (18.4–32.6)	−5.1	24.2 (18.1–31.2)	0.4	NS
Parathormone, pg/mL	55.5 (42.5–67.8)	−11.2†	53.3 (41.2–66.9)	5.5	< 0.001
Calcitonin, pg/mL	5.8 (4.3–7.7)	−1.5	5.6 (4.4–7.9)	−1.8	NS
Osteocalcin, ng/mL	9.0 (4.2–11.9)	−12.7‡	9.3 (4.6–11.2)	10.7‡	< 0.001
Bone alkaline phosphatase, UI/L	5.6 (0.7–7.6)	−14.0‡	5.5 (0.8–7.3)	15.1‡	< 0.001
β -crosslaps, ng/mL	0.46 (0.34–0.55)	−33.6§	0.48 (0.33–0.55)	13.4‡	< 0.001
Lumbar (L2–L4) BMD, g/cm ²	0.875 (0.784–0.954)	8.8†	0.880 (0.793–0.949)	−0.7	< 0.001
Lumbar (L2–L4) T-score	−2.55 (−2.93–−1.88)	21.0†	−2.42 (−2.90–−1.56)	−2.1	< 0.001
Left hip (femoral neck) BMD, g/cm ²	0.665 (0.604–0.752)	5.5†	0.653 (0.600–0.743)	−1.1	< 0.01
Left hip (femoral neck) T-score	−2.47 (−3.29–−1.63)	12.4†	−2.45 (−3.25–−1.79)	−2.7	< 0.01
Total body BMD, g/cm ²	1.050 (1.008–1.117)	4.1‡	1.059 (1.012–1.121)	−1.1	< 0.05
Total body T-score	−1.19 (−1.76–−0.46)	7.4‡	−1.22 (−1.73–−0.52)	−2.9	< 0.05
Methylprednisolone dose, mg/d	10.1 (7.9–12.0)	−32.9§	10.2 (8.1–11.6)	−29.1§	NS¶

*Values given as median (IQR), unless otherwise indicated. LVRS = lung volume reduction surgery; RR = respiratory rehabilitation; SGRQ = St. George Respiratory Questionnaire; NS = not significant.

†Intragroup significance, $p \leq 0.01$.

‡Intragroup significance, $p \leq 0.05$.

§Intragroup significance, $p \leq 0.001$.

||Value for subset of patients who were continuing to receive oral steroid therapy after undergoing surgery.

¶Value for subset of patients who were continuing to receive oral steroid therapy after undergoing surgery compared to patients in the respiratory rehabilitation group.

After respiratory rehabilitation therapy, statistical improvements were found only for some respiratory variables, whereas nutritional, hormonal, and bone-related variables showed a mild but significant worsening (Table 1). BMD and T-scores did not statistically differ from baseline values in every district, as well as in the osteoporosis rate (48 to 49%) and the osteopenia rate (35 to 34%).

Intergroup Evaluation

At baseline, no statistical differences were found between the surgical and rehabilitation groups in respiratory function and bone-related parameters. Twelve months after treatment, the patients who had undergone surgery showed a significant improvement in respiratory, nutritional, and bone-related parameters in comparison with the patients who had undergone rehabilitation (Table 1).

Steroid Therapy Evaluation

At baseline, the surgical and the respiratory rehabilitation groups were closely matched for median daily oral steroid (methylprednisolone) dosage (surgical group, 10.1 mg/d [IQR, 7.9 to 12.0 mg/d]; respiratory rehabilitation group, 10.2 mg/d [IQR, 8.1 to 11.6 mg/d]). After surgery, 19 of 40 patients discontinued oral steroid therapy (baseline dose, 9.9 mg/d; posttreatment change, -100% ; $p < 0.0001$) and persisted in this condition during the entire year of follow-up. The remaining 21 patients who underwent surgery significantly reduced the median daily oral steroid dosage (baseline, 10.1 mg/d; posttreatment change, -32.9% ; $p < 0.001$).

After respiratory rehabilitation, none of the patients was able to discontinue oral steroid therapy, although a significant reduction (-29.1% ; $p < 0.001$) in the median daily dosage was achieved. The median daily dosages of inhaled steroids and β_2 -agonists remained unchanged after treatment and during the entire year of follow-up (beclomethasone, 1.3 mg/d [IQR, 1.1 to 1.4 mg/d]; budesonide, 620 $\mu\text{g}/\text{d}$ [IQR, 550 to 700 $\mu\text{g}/\text{d}$]; salbutamol, 365 $\mu\text{g}/\text{d}$ [IQR, 320 to 390 $\mu\text{g}/\text{d}$]; formoterol, 36 $\mu\text{g}/\text{d}$ [IQR, 27 to 48]).

At baseline, no statistical difference was found among the two subsets of the surgical group and the respiratory rehabilitation group, in terms of respiratory, nutritional, and bone-related parameters or oral steroids dosage.

After surgery, the patients who discontinued oral steroid therapy exhibited a more significant improvement than those who continued receiving oral steroid therapy in terms of nutritional and bone-related parameters. Similarly, the patients who continued to receive oral steroid therapy experienced significant improvements in respiratory, nutritional, and bone-

related variables compared to patients who underwent respiratory rehabilitation. The changes in oral steroid dosage in these two groups were not significant (Fig 1).

Correlation Analysis

In the surgical group, the improvement in respiratory function was positively correlated with the amelioration of nutritional status. Anthropometric variables correlated with the levels of bone turnover markers; namely, the increment of fat-free mass with the reduction of osteocalcin ($\rho = -0.54$; $p = 0.04$), bone alkaline phosphatase ($\rho = -0.57$; $p = 0.01$), and β -crosslaps ($\rho = -0.65$; $p = 0.003$).

Significant correlations were found between the increase in lumbar BMD and the changes in the following parameters: residual volume (RV) [$\rho = -0.51$; $p = 0.02$]; DLCO ($\rho = 0.52$; $p = 0.01$); body mass index ($\rho = 0.50$; $p = 0.04$); fat-free mass ($\rho = 0.52$; $p = 0.01$); bone alkaline phosphatase ($\rho = -0.42$; $p = 0.05$); β -crosslaps ($\rho = -0.61$; $p = 0.001$); and methylprednisolone ($\rho = -0.41$; $p = 0.01$).

DISCUSSION

Declining bone mass and osteoporosis are common findings in patients with severe emphysema. The etiology is multifactorial, as follows: persistent flogosis²¹; chronic tissue hypoxia^{22,23}; impaired respiratory dynamics³; prolonged therapy with oral and inhaled steroids and β_2 -agonists; and secondary hormonal and biochemical alterations.⁷⁻¹² These factors favor a state of hypermetabolism that rapidly turns into catabolism with tissue depletion, including fat-free mass and bone tissue.⁵

Lung volume reduction surgery provides immediate and prolonged improvement of static volumes, exercise capacity, and quality of life over maximal medical therapy, including rehabilitation.^{14-16,24,25} Christensen et al²⁶ showed that weight gain after surgery was correlated with amelioration in gas exchange capacity. Nezu et al²⁷ demonstrated that the recovery of fat-free mass was due to augmented tissue oxygen delivery subsequent to a reduction in breathing workload. Takayama et al²⁸ showed that the improvement of pulmonary and nutritional parameters could be related to the reduction of the oxygen cost of breathing. Our group showed that lung surgery can restore normal body weight and body composition,²⁹ and can improve right ventricular function.³⁰ All of these changes appeared to correlate with the surgical reduction of lung RV.

In this study, we observed that surgery significantly improved BMD, especially in the districts that

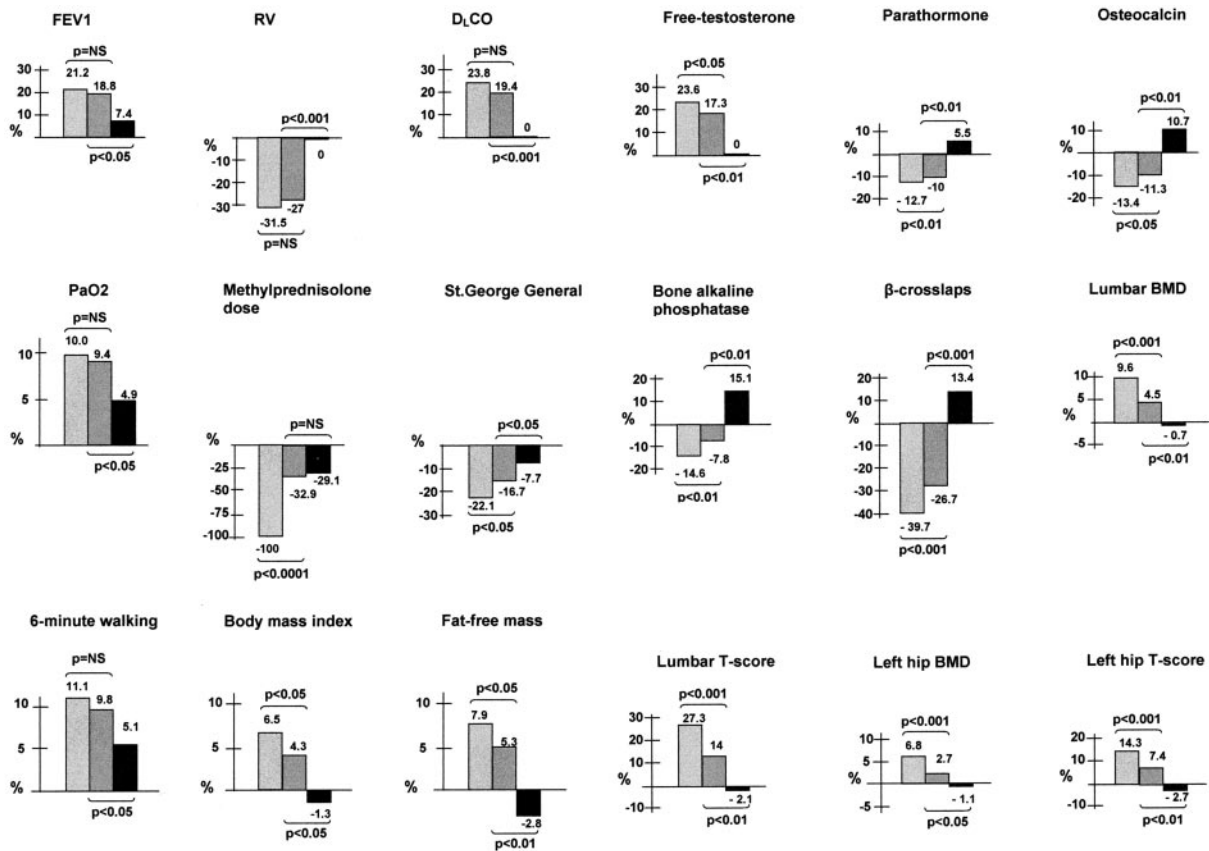


FIGURE 1. Patients selected for lung volume reduction surgery. Patients discontinuing oral steroid therapy = light gray column; patients continuing oral steroid therapy = dark gray column; respiratory rehabilitation = black column. The median 12-month posttreatment percentage changes and intergroup comparisons of the main respiratory, nutritional, and bone-related parameters. The p values are indicated near the bracket spanning the two columns being compared.

were at higher risk of fracture, with a reduction of T-scores and osteoporosis rates. Correlation analysis suggested that postoperative improvement of respiratory function positively influenced metabolism and nutritional status, thus affecting bone turnover and mineral content. In particular, lumbar BMD seemed directly correlated with the surgical reduction of RV and the amelioration of gas exchange and fat-free mass.

We hypothesized that lung volume reduction surgery increases gas exchange and oxygen availability in tissue, including bone tissue, by recruiting new anatomic spaces and supplementary pulmonary microcircles.^{26–30} Furthermore, the reduction of RV and thoracic hyperinflation favors the recuperation of proper muscle respiratory dynamics, thus decreasing physical and energetic overload^{14–16} and reversing the hypermetabolic-catabolic condition. The restored respiratory function might induce a more physiologic biochemical and metabolic pattern with an improvement of nutritional status. These events positively influence bone metabolism, as suggested

by the correlation between fat-free mass and bone turnover markers. The changes in bone-related hormone levels, especially those of free testosterone and parathormone, also contribute to bone anabolism and mineral preservation. In addition, the regained capacity of performing physical activity enhances bone deposition. Bone turnover markers showed a reduction in both the deposition and resorption phases with a relative prevalence of the latter, favoring a state of “bone metabolic resting and saving.” The osteoblastic and osteoclastic activity appears to reverse to a positive balance that slowly improves mineral density.

Lung volume reduction surgery seemed to improve bone metabolism and mineral content, whereas respiratory rehabilitation did not. After surgery, 19 patients discontinued therapy with oral steroids and showed the most significant improvements, confirming the well-known negative effects of oral steroids on nutritional, hormonal, and bone-related variables. Despite continuing therapy with oral steroids, the remaining 21 patients who under-

went surgery showed significant improvements compared to patients treated only with respiratory rehabilitation. According to this observation, we hypothesized that surgery contributed *per se* to the restoration of BMD.

Respiratory rehabilitation therapy, despite the reduction in oral steroid therapy, did not modify pulmonary static volumes, and produced a mild improvement in respiratory dynamics and gas exchange.^{16,24,25} Both the persistent hypermetabolic-catabolic condition and the poor nutritional status were obstacles in the restoration of physiologic bone metabolism and mineral density.

The limitations of our study are the nonrandomized nature of the trial, although the homogeneity at baseline of the two arms of the study group was statistically proven. The relatively small sample size did not allow appropriate dose-dependent and categorical analyses for oral steroid therapy. The possible interference of inhaled β_2 -agonist therapy on bone metabolism was only marginally considered. The role of metabolic hormones and inflammation mediators in the systemic complications of COPD was not investigated. The results provided are limited to a short period of observation, and the long-term effects of surgery on bone metabolism are not available.

In conclusion, we have demonstrated significant improvement in BMD and related T-scores after lung volume reduction surgery in patients with severe emphysema. These improvements occurred despite patients continuing to receive oral steroid therapy, and they were not found in patients who had been treated with respiratory rehabilitation. The increase in BMD correlates with RV, DLCO, and fat-free mass, suggesting that the restorations of respiratory dynamics, gas exchange, and nutritional status induce a “bone metabolic resting and saving.” The increase in bone mass and the reduction of osteoporosis suggest a new mechanism for clinical improvement after surgery.

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