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# Mineral Status of COPD Patients under Long-Term Inhaled Corticosteroid Therapy

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## Abstract

**Purpose:** The aim of this study was to determine the mineral status of mandibles, femurs, and spines in chronic obstructive pulmonary disease (COPD) patients under long-term inhaled corticosteroid therapy.
**Materials and Methods:** Pulmanory function tests were conducted on patients (n = 30) with COPD under inhaled corticosteroid therapy for at least 1 year. The results were compared to sex- and age-matched controls (n = 30). Analyses of blood gases were also carried out relative to COPD, and bone mineral densities (BMD) of the mandible, lumbar spine, femoral neck, trochanter, and Ward's triangle were also measured by dual-energy X-ray absorptiometry (DEXA). Levels of serum osteocalcin, alkaline phosphatase, calcium, phosphorus, and cortisol were also assessed.
**Results:** In accordance with the Global Initiative for Chronic Obstructive Lung Disease criteria, 8 of the COPD patients had moderate, 11 patients had severe, and 11 patients had very severe forms of the disease. All BMD measurements were lower in the COPD patients than in the control group. The serum osteocalcin levels in COPD patients were significantly lower than those in the control group ($p < 0.0001$). Serum calcium ($p < 0.004$) and cortisol levels ($p < 0.026$) in the COPD patients were also significantly lower than those in the control subjects. Although serum alkaline phosphatase level was higher and the phosphorus level was lower in the treatment group than in the control group, the differences were not statistically significant.
**Conclusion:** Regular evaluation of the biochemical markers of bone metabolism and BMD would be helpful for detecting any detrimental changes of bone in COPD patients under long-term inhaled corticosteroid therapy. In this study, mandibular BMD was observed to be lower in COPD patients under long-term inhaled corticosteroid therapy than in healthy subjects. Thus, dental implant treatment may require preventive measures in COPD patients under long-term inhaled corticosteroid therapy.

Osteoporosis is characterized by microarchitectural deterioration of the bone tissue, which leads to increased bone fragility and risk of fracture.[1] There are numerous factors in the etiology of osteoporosis,[2,3] one of which is long-term systemic corticosteroid therapy.[4-6] Corticosteroids decrease calcium absorption and upset the balance of bone metabolism through accelerating osteoclast-mediated bone resorption and reducing osteoblast-mediated bone formation.[5]

Although the adverse effects of orally administered corticosteroids on bone metabolism is well established, the literature on the effects of inhaled corticosteroids on the mineral status of bone is controversial.[7-10] Studies[11-14] have shown that bone mineral density (BMD) of the femur and lumbar vertebrae were reduced following long-term use of inhaled corticosteroids; however, Boulet et al[15] and Johnell et al[16] found that BMD of the hip and lumbar vertebrae were similar in the corticosteroid-treated and control groups of patients.

Inhaled corticosteroids can be recommended for advanced chronic obstructive pulmonary disease (COPD) to reduce the rate of deterioration in the patients' health status and

frequency of exacerbations.[17] Although inhaled corticosteroids are thought to directly affect the airway mucosa, these drugs are also absorbed from bronchii and alveolar surfaces. In addition, some portion of the drug deposited into the oropharynx may be swallowed and absorbed from the gastrointestinal tract, which may also exert systemic side effects. In addition, the effects of the disease process itself may have detrimental effects on bone quality.

It is well known that osteoporosis results in reduced mandibular bone mass as well as alterations of mandibular structure.[18-20] Jonasson[21] concluded that a significant relationship exists between BMD and mandibular alveolar bone mass, structure, and thickness. Quality of jaw bones may have an important role in diseases affecting the jaws, such as periodontal disease.[22] Investigators have found varying associations between osteopenia/osteoporosis, changes in attachment levels, loss of alveolar bone, and tooth loss in the aging population.[22] Krall et al[23] reported that BMD had positive correlations with the number of remaining teeth. Periodontal disease is a disease process resulting in alveolar bone and tooth loss. The decreased BMD in osteoporosis can affect all bones in the body, including the maxilla, mandible, and zygomatic processes. Thus, patients with oral bone loss due to osteoporosis-like conditions are at increased risk for tooth loss.[23] Should a disease process or treatment regimen targeting bone formation or bone resorption markedly disturb bone remodeling at the implant site, the osseointegration of dental implants could be at risk. It has been shown that osteoporotic bone may affect the healing period of bone tissue after the insertion of dental implants.[24-26] Blomqvist et al[27] directly implicated osteoporosis as a risk factor for implants in lesser quality bone. A number of studies have also indicated that implant survival in less dense bone was reduced.[28-31] Beer et al[32] showed a strong positive correlation between BMD and insertion torque for certain implant and surgical procedures. With more research, positive or negative predictions of achievable insertion torque because of decreased BMD in COPD patients under long-term inhaled corticosteroid therapy could be made preoperatively. This could influence implant loading protocols at the time of implant placement in COPD patients under long-term inhaled corticosteroid therapy.

Many patients with low or high BMD are not diagnosed adequately. Systemic diseases affecting bone density may influence the disease process or outcome of the implant treatment related to edentulous and partially edentulous jaws.[33] Early evaluation of the bone quality in COPD patients under long-term inhaled corticosteroid therapy may enable clinicians to take preventive measures.

The BMD of various sites, including the mandible, spine, and proximal femur,[34-37] and the effect of corticosteroids on mandibular implants and cumulative survival rates associated with osseointegration have also been studied by other authors[38-40]; however, the authors did not find any study in the literature relative to both mandibular and skeletal BMD in COPD patients under long-term inhaled corticosteroid therapy. The purpose of this study was to determine the BMD of various skeletal sites including the mandible, lumbar spine, and proximal femur, and to investigate any correlations in BMD of different regions of bone in COPD patients under long-term inhaled corticosteroid therapy.

## Materials and methods

Thirty patients with COPD using inhaled corticosteroids for at least 1 year were randomly selected from the clinics of the Pulmonary Medicine Department of Suleyman Demirel University Hospital. Half (n = 15) of the patients were taking budesonide (Pulmicort, Astra-Zeneca, Söderalje, Sweden) with a mean daily dose of 800 $\mu$g/day, and the other half were taking fluticasone propionate (Flixotide, GlaxoSmithKline, Evreux, France) with a mean daily dose of 1000 $\mu$g/day. The mean duration of treatment was 10 years (7.5 for budesonide, 12.7 for fluticasone propionate). The use of other treatments, such as short/long acting beta agonists, anticholinergics, theophylline, and as-needed antibiotics, was unrestricted in this study because they have no known effect on calcium metabolism. Patients with a history of any other disease or under any other medication (including oral and parenteral corticosteroid treatment during the previous 6 months) that may have influenced bone metabolism were excluded from the study.

The control group was also determined randomly and consisted of 30 sex- and age-matched patients with no pulmonary disease. None of these patients were taking any medications that could affect bone metabolism. All female patients were postmenopausal. Cigarette smoking status, age, body mass index (BMI), and the total cumulative doses of the medications were recorded for all patients. Twelve patients in both groups were nonsmokers. In the COPD group, 15 patients were former smokers, and 3 patients were current smokers (5 to 10 cigarettes/day). In the control group, 13 patients were ex-smokers, and 5 patients were current smokers (5 to 10 cigarettes/day). The groups were comparable with respect to age, gender, and BMI (Table 1).

Morning arterial blood samples were collected for blood gas analysis. For the COPD patients, these samples were taken at

**Table 1** Patient characteristics

| | Treatment group | | | Control group | | |
|---|---|---|---|---|---|---|
| Gender | Male (n = 20) | Female (n = 10) | Total (n = 30) | Male (n = 20) | Female (n = 10) | Total (n = 30) |
| Age | 68.1 (±10.2) | 61.7 (±11.8) | 65.9 (±11.0) | 67.3 (±9.2) | 64.2 (±6.5) | 66.2 (±8.4) |
| BMI (kg/m$^2$) | 23.2 (±3.7) | 25.5 (±4.2) | 24.0 (±3.9) | 24.7 (±2.0) | 25.8 (±3.6) | 25.1 (±2.6) |

BMI = body mass index.

least 45 minutes prior to oxygen treatment. The blood gases were assessed using Roche OMNI® C Analyzer (Roche Diagnostics, Mannheim, Germany).

Pulmonary function tests were measured three times at 9:00 a.m. according to the standards of the American Thoracic Society[41] using Spirovit SP-10 (Schiller, Baar, Switzerland). The spirometry units were calibrated daily. The best results of the pulmonary function tests were accepted for this study. Prediction equations for Forced Expiratory Volume in the first second (FEV1) and forced vital capacity (FVC) were used to adjust for height, age, and sex. Airflow obstruction was deemed to be present when the participant's FEV1:FVC ratio was less than 70%. Severity of the disease was determined on the basis of FEV1 measurements as follows: mild: FEV1 $\geq$80% predicted; moderate: 50% $\leq$FEV1 $<$80% predicted; severe: 30% $\leq$FEV1 $<$50% predicted; and very severe: FEV1 $<$30% predicted or FEV1 $<$50% predicted plus chronic respiratory failure (the criterias were used in the study according to GOLDCOPD 2003 report).[42]

Morning venous blood samples were taken to assess osteocalcin, alkaline phosphatase, calcium, phosphorus, and cortisol serum levels. Alkaline phosphatase, calcium, and phosphorus were analyzed spectrophotometrically by Abbott Aeroset, Automated Instrument Analyzer (Abbott Laboratories, Abbott Park, IL). Osteocalcin was measured using the Immulite immunometric assay, and the cortisol samples were analyzed using the Immulite chemoluminescence immunoassay (Diagnostic Products Corporation, Los Angeles, CA).

BMD (g/cm$^2$) was measured using dual-energy X-ray absorptiometry (DEXA) (Norland XR-46 bone densitometer with dynamic filtration; Norland Medical Systems, Inc., Fort Atkinson, WI). The densitometer was calibrated daily 30 minutes after turning the apparatus on. Quality control was performed using calibration standard and QC phantom. BMD scans of the AP lumbar spine (L2-L3), femur neck, Ward's triangle, and trochanter were analyzed using World Health Organization criteria for bone mass.[43] BMD of the mandible was carried out using the method described by Horner et al.[44] Variables for the COPD patients and control group were compared with Student *t*-test. To compare the parameters according to gender and smoking status, the Mann–Whitney U-test was performed when groups were subdivided. The Kruskal–Wallis test was performed to compare variables where patient groups were allocated according to the severity of disease and the two drug regimes used. The Pearson correlation coefficient was used to determine the linear relationships between variables.

## Results

All COPD patients had statistically significant decreased pulmonary function measurements compared to the control patients ($p < 0.0001$). The mean FEV1/FVC was 58.03 ($\pm$15.75) and percentage of FEV1 was 36.80 ($\pm$15.12) for the COPD patients compared to 83.65 ($\pm$7.15) and 95.30 ($\pm$14.89) in the control group, respectively. In accordance with the Global Initiative for Chronic Obstructive Lung Disease criteria,[34] 8 patients had moderate, 11 patients had severe, and 11 patients had very severe forms of the disease.

**Table 2** Biochemical measurements in the COPD patients and control group

| | Treatment group | Control group | *p* |
|---|---|---|---|
| Osteocalcin (ng/ml) | 5.51 ($\pm$5.71) | 12.37 ($\pm$8.15) | $<$0.0001 |
| Alkaline phosphatase (U/L) | 92.00 ($\pm$49.12) | 75.57 ($\pm$22.94) | N/S |
| Calcium (mg/dl) | 9.03 ($\pm$0.65) | 9.46 ($\pm$0.43) | 0.004 |
| Phosphorus (mg/dl) | 3.11 ($\pm$0.55) | 3.27 ($\pm$0.58) | N/S |
| Cortisol ($\mu$g/dl) | 8.63 ($\pm$7.11) | 12.31 ($\pm$5.20) | 0.026 |

COPD = chronic obstructive pulmonary disease; N/S = nonsignificant.

Arterial blood gas analysis showed that the oxygen saturation and $PaO_2$ were significantly lower in COPD patients [88.63% ($\pm$7.64) and 57.22 mmHg ($\pm$13.99)] compared to the control group [92.63% ($\pm$8.35) and 69.90 mmHg ($\pm$12.02)], ($p = 0.006$, $p < 0.0001$), respectively. In addition, COPD patients had high levels of $PaCO_2$ and $HCO_3$ [37.53 mmHg ($\pm$7.44) and 26.78 ($\pm$8.38)] compared to the control group [32.66 ($\pm$4.31) and 22.38 ($\pm$2.55)] ($p = 0.003$, $p = 0.008$), respectively. BMD of all the skeletal sites studied was positively correlated with $PaO_2$ and negatively correlated with $PaCO_2$ ($p \leq 0.04$).

The biochemical measurements are listed in Table 2. In COPD patients, the mean level of serum osteocalcin was lower than in the control group ($p < 0.0001$). Serum calcium and cortisol levels in the COPD patients were also significantly lower than those in the control subjects. Although serum alkaline phosphatase level was higher and the phosphorus level was lower in the treatment group compared to the control group, the differences were not statistically significant. Serum osteocalcin levels were positively correlated with serum calcium and cortisol levels, whereas serum alkaline phosphatase levels were negatively correlated with serum calcium levels. In addition, serum calcium levels were correlated with oxygen levels, oxygen saturation, and mandibular BMD.

The BMD (g/cm$^2$) of the mandible, proximal femur, and lumbar spine can be seen in Figure 1. All BMD measurements (g/cm$^2$) were lower in the COPD patients than in the control group. The difference in the BMD values was statistically significant for male patients (mandible, $p = 0.003$; femoral neck, $p = 0.001$; femoral trochanter, $p < 0.0001$; femoral Ward's triangle, $p = 0.003$; and lumbar spine, $p = 0.002$). Although female COPD patients also had lower BMD values, they did not reach statistical significance. There was a positive correlation between BMD values of all the skeletal sites ($p < 0.0001$), except in the mandible.

No significant difference was found among the variables when COPD patients were subdivided according to the two drug regimens (except $PaCO_2$ and $HCO_3$, $p = 0.01$ for both) and the severity of the disease.

## Discussion

The results of this study demonstrated that BMD values of the spine and hip, as well as the mandible, were reduced in COPD patients with long-term inhalation corticosteroid therapy (budesonide, fluticasone propionate) when compared to

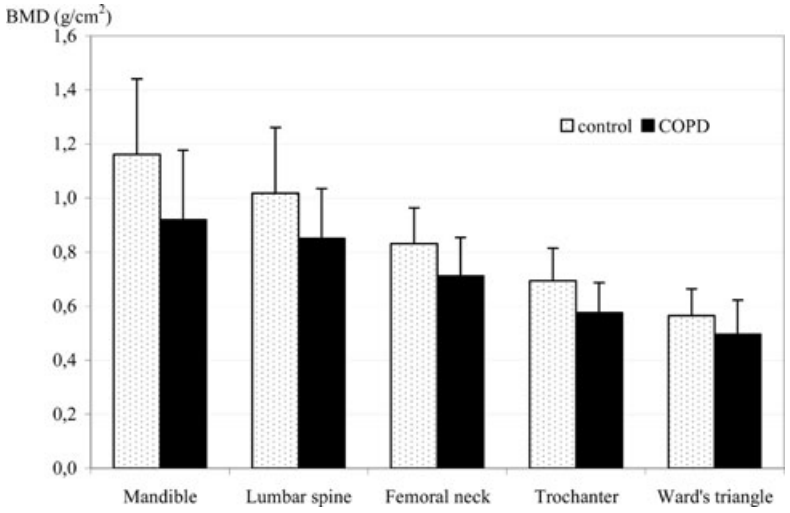


**Figure 1** BMD (g/cm$^2$) of the mandible, lumbar spine, and proximal femur in the COPD patients and control group. COPD = chronic obstructive pulmonary disease; BMD = bone mineral density.

control patients. Decreased BMD may be due, in part, to long-term administration of inhaled corticosteroids. Several studies have shown that the BMDs of the femur and lumbar vertebrae were reduced following long-term inhaled corticosteroid therapy.[11-14] Johnell et al[16] found no significant changes in BMD in the spine or femur of mild COPD patients using 800 $\mu$g/day budesonide (up to 36 months of treatment). Wong et al[13] reported a negative correlation between cumulative doses of inhaled corticosteroids and BMDs in patients with asthma using a median cumulative dose of 876 mg corticosteroids for a median duration of treatment period of 6 years.

Biochemical markers of bone turnover provide information on the processes of both bone resorption and bone formation. In the present study, low levels of serum osteocalcin, considered to be the marker of choice for bone formation,[10] were found in COPD patients. Furthermore, serum calcium levels were positively correlated with decreased osteocalcin levels and BMDs of the mandible. Fluticasone propionate, when administered in higher doses and for longer periods of time, as in the present study, also led to reductions in osteocalcin levels.

Serum alkaline phosphatase is another commonly used biochemical marker of bone formation. The findings on alkaline phosphatase in this study were consistent with other studies that showed similar serum alkaline phosphatase levels in patients receiving inhaled corticosteroids when compared with patients not receiving steroid treatment.[10,11]

In this study, the finding that COPD patients had low levels of serum cortisol implied that long-term use of inhaled corticosteroids leads to suppression of adrenocortical function.[11] In addition, suppression of cortisol was demonstrated to be associated with decreased levels of osteocalcin, which may further indicate the adverse effect of long-term inhaled corticosteroids on bone metabolism.

In this cross-sectional study, patients were selected from those patients taking corticosteroids long-term (the mean duration of the treatment was 10 years). In addition, 22 patients had severe/very severe forms of the disease. Inhaled corticosteroids are often used for advanced COPD patients to reduce the rate of deterioration in their overall health status. Therefore, for ethical reasons, the control group was not selected from COPD patients not treated with corticosteroids. Hence, from the findings of this study, the reduction in the BMDs in the experimental group cannot be attributed solely to the inhaled corticosteroid treatment, because the disease itself may be a significant risk factor for the development of osteoporosis. Iqbal et al[12] reported that although the prevalence of osteoporosis was higher (ninefold) after chronic glucocorticoid therapy, patients with chronic lung disease who had never been treated with glucocorticoids had substantial (fourfold) risk of osteoporosis. In the present study, BMD values of all skeletal sites were positively correlated with $PaO_2$ and negatively correlated with $PaCO_2$ values. Low tissue oxygenation in patients with COPD may affect bone metabolism and may contribute to the decreased BMD values seen in this study.

Several studies showed that mandibular BMDs were positively correlated with other skeletal BMDs, such as lumbar vertebrae and femur, in healthy populations.[18,20,44] Mandibular BMD was correlated with other skeletal BMDs in populations of normal[19] and osteoporotic women.[37] In the present study, although an association was found in the BMD of all skeletal sites studied, the mandibular findings were not correlated with other sites. A possible explanation for the conflicting results may be the effect of mastication on the jaw bone density. Krall et al[23] reported that the loss of BMD at multiple skeletal sites was associated with the loss of teeth in healthy postmenopausal women.

This study showed that both skeletal and mandibular BMDs were reduced in COPD patients under long-term inhaled corticosteroid therapy. Many clinicians and researchers have observed that the osseointegration of dental implants is slower in osteoporotic subjects.[24,27,38,39] A decreased capacity of osteoblasts, isolated from osteoporotic bone, to proliferate in response to systemic or locally released osteotropic factors has also been observed.[2,3] These changes have been observed in different in vivo studies performed in animal models by decreased trabecular bone volume and other static and dynamic

histomorphometric parameters as well as bone-to-implant contact around implants.[31]

Keller et al showed that osseointegration was possible in osteoporosis-like bone, but because the regenerative capacity of bone was diminished, longer healing periods were necessary to obtain adequate osseointegration.[38] The healing period should be extended by 2 months, that is, 8 versus 6 months in the maxilla and 6 versus 4 months in low density mandibular bone.[25,26] Implant designs that assure stable bone–implant interfaces at implant placement should be selected to overcome the inability of less dense osteoporotic bone to stabilize the implants. By analogy, therefore, it may be prudent to assure primary fixation of self-tapping threaded implants without cortical countersink procedures.[33]

The findings of the present study showed that although COPD patients had lower BMDs for both genders, the difference was not statistically significant for female patients for all sites studied. In this study, patients were matched for gender, age, menopausal state, and BMI; however, other confounding factors may have a role in bone density. In addition, the smaller number of female patients (10 female versus 20 male patients in both groups) used in this study may also be responsible for the statistical significance of the results. Further studies using larger groups are required.

## Conclusion

The results for COPD patients under long-term inhaled corticosteroid treatment in this study indicate that they should be biochemically and densitometrically monitored regularly to detect any impairment in BMD. In COPD patients under long-term inhaled corticosteroid therapy, low density mandibular bone may necessitate some preventive measures such as a longer healing period after surgery, selection of implant designs that assure stable bone-implant placement, and primary fixation of self-tapping implants without countersink procedures prior to and during dental implant treatment.

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