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ORIGINAL ARTICLE

Oral health in patients on inhaled corticosteroid treatment

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OBJECTIVE: The aim of this study was to investigate the effects of long-term inhaled corticosteroids on bone mineral density (BMD) of the mandible in relation with the tooth loss.

DESIGN: Cross sectional analytic study.

SUBJECTS AND METHODS: Patients (*n* = 30) with chronic obstructive pulmonary disease under inhaled corticosteroid therapy for at least 1 year were compared with sex- and age-matched healthy controls (*n* = 30). BMD of the mandible was measured by dual-energy X-ray absorptiometry. The clinical examination included recording the number of teeth present together with periodontal condition. Levels of serum osteocalcin, alkaline phosphatase, calcium, phosphorus and cortisol were also assessed.

RESULTS: BMD of the mandible in patients on corticosteroid treatment was significantly lower than that in the control group (*P* = 0.001). Patients under treatment had more missing teeth than the control group but the difference did not reach statistical significance. The two groups exhibited similar clinical parameters of periodontal condition. Significantly lower levels of osteocalcin (*P* < 0.0001), calcium (*P* = 0.004) and cortisol (*P* = 0.03) were observed in the patients on corticosteroid treatment.

CONCLUSION: Long-term use of inhaled corticosteroids may impair bone metabolism and lead to a marked decrease in the mandibular BMD.

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Keywords: corticosteroids; bone mineral density; mandible; periodontitis; tooth loss

Introduction

Osteoporosis is one of the serious adverse effects of long-term systemic corticosteroids (Gennari, 1993). Disturbed bone metabolism in osteoporosis leads to low bone mineral density (BMD) which, in general, is a risk factor for spontaneous fractures. The decreased BMD of the jaws may be particularly important as they are exposed to constant masticatory forces and they retain teeth of which stability is related to the quality of bone. Thus, impaired bone density of the jaws may be a risk factor for tooth loss. It has been reported that patients with low BMD in various sites of the body skeleton had less teeth compared with the normal population (Kribbs, 1990; Krall *et al*, 1996; Taguchi *et al*, 1999).

Corticosteroids have been widely used in the management of chronic obstructive pulmonary disease (COPD) and asthma. Inhaled corticosteroids aimed to have a direct effect on the lungs. However, the molecules pass into the systemic circulation through alveoli and long-term use of inhaled corticosteroids may lead to osteoporosis. A number of studies have shown that inhaled corticosteroids caused a reduction in BMD of the non-oral sites such as lumbar spine and femur (Hanania *et al*, 1995; Wong *et al*, 2000; Sivri and Coplu, 2001). In addition, low levels of bone formation markers were reported in patients under inhaled corticosteroid treatment (Hanania *et al*, 1995; Meeran *et al*, 1995; Wisniewski *et al*, 1997). A reduction in the bone mineral content of mandible following systemic corticosteroid treatment was also reported (von Wowern *et al*, 1992). However, the extent of the bone loss in the mandible of patients using inhaled corticosteroids remained unknown. Therefore, the aim of this study was to investigate the BMD of the mandible in relation with the number of teeth retained in COPD patients under long-term inhaled corticosteroid treatment.

Subjects and methods

Patient selection

Thirty patients with COPD, who attended to the Clinics of pulmonary medicine department of Süleyman Demirel University Hospital and have been using inhaled corticosteroid for at least 1 year, were participated in this cross-sectional study. Patients with a history of any other disease or under any medication (including oral corticosteroid treatment) that may influence bone metabolism were excluded from the

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study. Of the 30 patients, 20 were male (mean age, 68.1 ± 10.2) and 10 were female (mean age, 61.7 ± 11.9). Half of the patients were under budesonide (0.2–0.8 g day^{-1}; Astra-Zeneca Sődertălje, Sweden) while the other half were under fluticasone propionate (0.5–2 g day^{-1}; GlaxoSmithKline, Evreux, France) treatment. The drugs used were at clinically equipotent doses. The total cumulative dose of the medication was 6.8 g (±7.0) for fluticasone propionate and 1.3 g (±1.8) for budesonide. Respiratory function of the COPD patients was estimated by calculating the ratio of forced expiratory volume (FEV) after 1 s (FEV_1)/forced vital capacity (FVC). Airflow obstruction was deemed to be present when the participant's FEV1 to FVC ratio was <70%. Severity of airflow obstruction was determined on the basis of FEV_1 measurements, as follows: mild – $FEV_1 \geq 80\%$ of predicted; moderate – FEV_1 50–80% of predicted; severe – FEV_1 30–50% of predicted; and very severe – FEV_1 <30% of predicted (GOLD Workshop Report, 2003). Accordingly, eight patients had moderate, 11 patients severe and 11 patients very severe form of the COPD.

Control group was consisted of sex- and age-matched 30 subjects including 20 male (mean age, 67.3 ± 9.2) and 10 female (mean age, 64.2 ± 6.5) with no disease or under no medication that may affect bone metabolism.

All the female patients were postmenopausal. The two groups were comparable with respect to gender, age, body mass index (BMI) and smoking status (Table 1).

Measurement of BMD of the mandible

The BMD of the mandible was measured by dual-energy X-ray absorptiometry, DXA (Norland XR-46; Norland Medical Systems Inc., Fort Atkinson, WI, USA). BMD measurements were performed on the body of mandible which produces greater sensitivity and specificity compared with the ramus and symphysis regions, as described by Horner *et al* (1996). Patients were positioned on their side with the neck extended to avoid the superimposition of cervical spine. Mandible was scanned in a rectilinear manner starting from 1 cm above the temporomandibular joint through the whole of the mandible on one side. The image of the contralateral side was superimposed. When both sides of the mandible were not superimposed because of positioning error of the mandible, the scanning was repeated. After DXA scan images were recorded and displayed on the computer monitor, manual analysis of these scans was carried out using rectangular customized regions placed over the body of mandible extending from anterior ramus to the parasymphyseal region. The size of the selected regions was adapted to conform to the shape of the mandible of each patient. For dentate patients, attention was paid to avoid selected regions from incorporating roots of teeth. BMD (g cm^{-2}) of the selected region was calculated by lumbar spine computer software. Mandibular DXA scans were analysed only by one independent investigator, who was blind to the patients' status, to minimize the inter-observer variations. The reproducibility of the measurement system was assessed by repeating the analysis three times for each image.

Table 1 Patient characteristics

	Patient group (n = 30)	*Control group (n = 30)*
Male:female	20:10	20:10
Age	65.9 (±11.0)	66.2 (±8.4)
Body mass index (kg m^{-2})	24.0 (±3.9)	25.1 (±2.6)
Smoking status	Non-smoker: 12 Ex-smoker: 15 Current smoker: 3	Non-smoker: 12 Ex-smoker: 13 Current smoker: 5

Dental and periodontal parameters

The number of remaining teeth, except third molars, was recorded at the time of oral examination. To assess oral hygiene and periodontal condition, measurements of plaque index (PI) (Silness and Loe, 1964), gingival index (GI) (Loe and Silness, 1963) and probing pocket depth (PPD) were carried out for all teeth present. In addition, community periodontal index of treatment need (CPITN) was determined (Ainamo *et al*, 1982).

Biochemical measurements

Venous blood samples were obtained from all study groups in the morning to assess serum levels of osteocalcin, alkaline phosphatase, calcium, phosphorus and cortisol. The levels of alkaline phosphatase, calcium and phosphorus in the samples were determined spectrophotometrically using an automated instrument analyser (Abbott Aeroset; Abbott Laboratories, Chicago, IL, USA). Osteocalcin and cortisol levels in the serum samples were measured using the Immulite immunometric assay (Diagnostic Products Corporation, Los Angeles, CA, USA) and the Immulite chemiluminescence immunoassay (Diagnostic Products Corporation), respectively.

Statistical analysis

The mean measures per patient were calculated and the subject was taken as the statistical unit. The Kolmogorov–Smirnov test was used to check homogenicity of distribution prior comparison of the two groups. Comparisons of the patient and control groups for all variables were performed using the student *t*-test. Mann–Whitney *U*-test was performed when groups were subdivided in order to compare the parameters according to edentulousness, gender, smoking status. Kruskal Wallis test was performed to compare variables when patient group was allocated according to the severity of disease and the two drug regime used. Pearson correlation coefficient was used to determine linear relationship between all variables. Values of $P < 0.05$ were set as statistically significant.

Results

BMD of the mandible

Figure 1 shows a representative DXA image of the mandible of a patient. BMD measures of the two groups

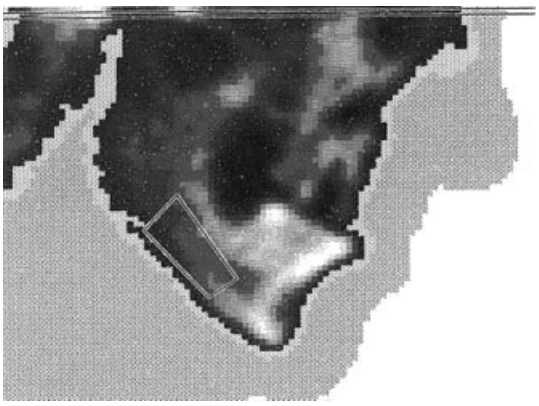

Figure 1 A representative mandibular DXA image

Table 2 Bone mineral density (g cm^{-2}) of the mandible

	Patient group	*Control group*	*P*-value
Edentulous	0.90 (±0.24)	1.21 (±0.32)	0.004
Dentate	0.96 (±0.29)	1.11 (±0.23)	N/S
Male	0.95 (±0.21)	1.19 (±0.25)	0.003
Female	0.87 (±0.36)	1.11 (±0.34)	N/S
Non-smoker	0.87 (±0.27)	1.17 (±0.30)	0.022
Ex-/current-smoker	0.96 (±0.25)	1.16 (±0.27)	0.029
Total	0.92 (±0.26)	1.16 (±0.28)	0.001

COPD patient group comprised 12 dentate patients and control group comprised 16 dentate subjects. There were 20 male and 10 female patients in both groups. Twelve patients were non-smoker and 18 patients were ex- or current-smoker in both groups. Values are expressed as the mean (±s.d.).
N/S, not significant.

are listed in Table 2. The mean mandibular BMD was 0.92 in the COPD patients compared with 1.16 in the control subjects ($P = 0.001$). Although, COPD patients had lower BMD for both gender, it did not reach to the statistical significance for female patients ($P = 0.003$ for males and $P = 0.142$ for females). Similarly, the difference in BMD between the two groups was statistically significant for the edentulous patients ($P = 0.004$) but not significant in the dentate patients ($P = 0.136$). BMD levels of the mandible in the non-smoker and ex- or current-smoker COPD patients were statistically different from those in the control subjects ($P = 0.022$ and $P = 0.029$, respectively).

Mandibular BMD was positively correlated with serum calcium levels ($r = 0.365$, $P = 0.004$) whereas it was negatively correlated with alkaline phosphatase levels ($r = 0.515$, $P < 0.001$). However, no correlation was found between mandibular BMD and age of the subjects, the cumulative doses of the drugs and the severity of the disease. In addition, BMD was correlated neither with the number of teeth nor with the periodontal condition.

Dental and periodontal status

Sixteen COPD patients under corticosteroid treatment and 12 control subjects were edentulous. In addition, 18 patients in the COPD group had no teeth remained in the mandible as opposed to 14 subjects in the control group. The mean number of teeth retained in both jaws was 6 (±9) in the COPD patients and 8 (±8) in the controls. The mean number of teeth present in the mandible was 3 (±5) in the patient group and 5 (±5) in the control group. However, the differences were not statistically significant. A negative correlation was found between the number of teeth remained and the age of the patients ($r = 0.433$, $P = 0.001$), as expected.

In the 14 dentate COPD patients and 18 dentate control subjects, PI was 1.40 (±1.06) and 1.44 (±1.07); and GI was 1.27 (±1.03) and 1.22 (±1.1), respectively. PPD of the patient group was 3.41 (±0.87) while PPD of the control group was 3.23 (±0.68). Patients under corticosteroid treatment had a mean CPITN of 2.36 (±0.67) similar to the controls with a mean CPITN of 2.44 (±1.2). No statistically significant differences were found between the two groups for any clinical parameters.

Table 3 Biochemical measurements in the patient group with chronic obstructive pulmonary disease and the control group

	Patient group	*Control group*	*P*-value
Osteocalcin (ng ml^{-1})	5.51 (±5.71)	12.37 (±8.15)	0.000
Alkaline phosphatase (U l^{-1})	92.00 (±49.12)	75.57 (±22.94)	N/S
Calcium (mg dl^{-1})	9.03 (±0.65)	9.46 (±0.43)	0.004
Phosphorus (mg dl^{-1})	3.11 (±0.55)	3.27 (±0.58)	N/S
Cortisol (μg dl^{-1})	8.63 (±7.11)	12.31 (±5.20)	0.026

Values are expressed as the mean (±s.d.).

Biochemical measurements

Levels of bone formation markers and cortisol are listed in Table 3. Serum osteocalcin level in the COPD patient group was 5.51 ng ml^{-1} as opposed to 12.37 ng ml^{-1} in the control group, and the difference was statistically significant ($P < 0.001$). Serum calcium and cortisol levels in the COPD patients were also significantly lower compared with those in the control subjects ($P = 0.004$ and 0.026, respectively). Although serum alkaline phosphatase level was higher (92.00 U L^{-1}) and the phosphorus level was lower (3.11 mg dl^{-1}) in the COPD patient group compared with the control group (75.57 U L^{-1} and 3.27 mg dl^{-1}, respectively), the differences were not statistically significant.

Serum osteocalcin levels were positively correlated with serum calcium and cortisol levels ($r = 0.425$, $P = 0.001$ and $r = 0.286$, $P = 0.027$, respectively) whereas serum alkaline phosphatase levels were negatively correlated with serum calcium levels ($r = 0.363$, $P = 0.004$).

No statistically significant differences were found between all the variables when study group was subdivided according to the severity of the disease and the two drug regimen.

Discussion

It has been shown that long-term use of inhaled corticosteroids may lead to a reduction of BMD hence

increasing the risk of osteoporosis. Significant reductions in BMD of femur (Hanania *et al*, 1995) and lumbar spine in patients under long-term inhaled corticosteroid treatment were reported (Sivri and Coplu, 2001). Although adverse effects of systemically administered corticosteroid treatment on the mandibular bone have been demonstrated both by animal studies (Southard *et al*, 2000) and clinical trials (Olgaard *et al*, 1992; von Wowern *et al*, 1992), to our knowledge, the effects of inhaled corticosteroids on BMD of the mandible have not yet been investigated. This study showed, for the first time, that BMD of the mandible in COPD patients on long-term inhaled corticosteroid treatment was significantly lower than that in the control subjects ($P = 0.001$) which implies that long-term use of inhaled corticosteroids may also lead to a marked reduction in the mineral density of the mandibular bone.

The effects of corticosteroids are cumulative hence as the cumulative dose of the drug increases, decrease of the BMD is expected. However, different bone regions in the body may respond to corticosteroids at different manner. Sivri and Coplu (2001) reported that cumulative doses of inhaled corticosteroids negatively correlated with BMD of the lumbar spine but not of the femur. After adjusting for BMI and lung function, osteoporosis of the lumbar spine has been observed most frequently in patients receiving corticosteroids administered in multiple courses (Dubois *et al*, 2002). Furthermore, Olgaard *et al* (1992) showed that although significant reductions of the bone mineral content were observed in corticosteroid treated-nephrotic patients, the bone decay rates were significantly different at the mandible, forearm and lumbar spine. Southard *et al* (2000) induced osteoporosis in a rabbit model by injection of steroid and demonstrated that mandibular BMD decreased in relation to cumulative steroid dose. The route of the administration may contribute to the response of bone to steroids. A negative correlation between cumulative dose of the steroid and BMD was reported when the drug was administered in multiple courses but such a correlation was not found in continuous administration (Dubois *et al*, 2002). On the contrary, the present study showed that BMD of the mandible did not correlate with the cumulative dose of the inhaled corticosteroids. While this result may be due to the small sample size used, other factors such as masticatory function and the presence of teeth may also contribute to the level of BMD of the mandible. Our study showed that BMD of the mandible in the edentulous COPD patients was significantly lower than in the edentulous healthy controls. However, the finding of similar BMD levels of the dentate patients and control subjects may partly support the hypothesis that teeth might tend to keep BMD of the mandible constant.

Although not statistically significant, patients under corticosteroid treatment had fewer teeth remained compared with the control group. In addition, 16 patients under corticosteroid treatment were edentulous as opposed to 12 patients in the control group. Tooth loss has been associated with decreased BMD of the mandible and other sites of the skeleton. Kribbs (1990) reported that osteoporotic population had lower BMD of the mandible and less teeth compared with the normal population. An association between the number of teeth and mineral status of the bone was also reported in healthy postmenopausal women. Taguchi *et al* (1999) found that the number of posterior teeth was positively correlated with mandibular bone mass and BMD of the lumbar spine. In addition, an association between the femoral neck and lumbar spine BMD and the number of teeth was reported in healthy postmenopausal women (Krall *et al*, 1996). Tooth loss is influenced by many factors, however, mineral density of the mandible may also play a role in the stability of teeth in the alveolar socket. Hence, a decrease in the BMD may contribute to the resorption of tooth-supporting alveolar bone. In the present study, although no correlation was found between BMD of the mandible and the number of teeth, it may be speculated that decreased density of the mandibular bone may increase the risk of tooth loss.

Whether osteoporosis has any impact on the prevalence or intensity of periodontal disease has not been established in the literature. Similar levels of gingival bleeding, PPD, gingival recession and marginal bone level were found in women with and without osteoporosis (Kribbs, 1990; Lundstrom *et al*, 2001). On the contrary, significantly greater loss of attachment with no significant differences in PI and gingival bleeding was reported in osteoporotic women (von Wowern *et al*, 1994). In the present study, no significant differences in the periodontal parameters were found between the patients on long-term inhaled corticosteroid therapy and healthy control subjects. In parallel, high dose systemic corticosteroid treatment used for multiple sclerosis (Safkan and Knuuttila, 1984) and renal disease (von Wowern *et al*, 1992) did not cause any significant changes in periodontal status.

Microbial dental plaque is the primary aetiological factor for periodontal disease, and oral hygiene appears to play the most important role in the establishment of the inflammatory process along with the host response. In this study, both COPD patients and control subjects had similar PI levels. However, several contributing factors including quality of bone should be taken into account in the progress of the periodontal disease. It may be also speculated that once the periodontal problems occur, the teeth may be lost easier in patients with low BMD. Ronderos *et al* (2000) have shown that clinical attachment level was associated with femoral BMD when high level of calculus was present. Furthermore, Klemetti *et al* (1994) have stated that individuals with high skeletal BMD appear to retain their teeth with deep periodontal pockets as opposed to those with low BMD.

Scannapieco and Ho (2001) suggested that COPD may be associated with periodontitis. This implies the possibility that patients with COPD may be at risk of developing periodontitis and consequent tooth loss. In the present study, COPD patients who were not under corticosteroid treatment were not participated for ethical reasons. However, the patient group tended to have less teeth than did the control subjects, although there

were no significant differences in periodontal parameters between the two groups. Moreover, low number of remaining teeth made it difficult to speculate whether tooth loss had occurred because of periodontal disease or any other genetic and behavioural risk factors.

Bone metabolism depends on the equilibrium between bone formation by osteoblasts and bone resorption by osteoclasts. Biochemical markers of bone turnover provide information on the processes of both bone resorption and bone formation. Osteocalcin has been considered to be the marker of choice for osteoblast function and, low levels of serum osteocalcin may reflect suppression of bone formation by inhaled corticosteroids (Lipworth, 1999). In this study, the finding that significant reduction of serum osteocalcin concentrations was found in patients under inhaled steroid treatment confirms previously published studies of Kerstjens *et al* (1994), Hanania *et al* (1995), Meeran *et al* (1995) and Wisniewski *et al* (1997). Serum alkaline phosphatase is another commonly used biochemical marker of bone formation. However, it is not as sensitive as osteocalcin and tended to be within normal limits in patients with osteoporosis (National Institutes of Health, Osteoporosis and Related Diseases, updated 2003). Our findings on alkaline phosphatase is consistent with other studies that showed similar serum alkaline phosphatase levels in patients receiving inhaled corticosteroids with patients not receiving steroid treatment (Kerstjens *et al*, 1994; Hanania *et al*, 1995; Meeran *et al*, 1995; Wisniewski *et al*, 1997).

In this study, the finding that COPD patients had low levels of serum cortisol implies that long-term use of inhaled corticosteroids have systemic activity and lead to suppression of adrenocortical function (Hanania *et al*, 1995; Wilson and Lipworth, 1999). 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.

Mineral structure of bone is mainly made up by calcium and phosphorus. Although both minerals were in lower concentrations in patients under corticosteroid treatment, only levels of serum calcium showed a statistically significant difference. Demineralization of the bone by long-term corticosteroid treatment was stated to be mainly due to the reduced intestinal absorption of calcium (Gennari, 1993). Significantly low levels of serum calcium found in this study also reflect the disturbance of calcium absorption. Furthermore, serum calcium levels were found to be correlated with osteocalcin levels and BMD of the mandible. Therefore, a diet rich in calcium and vitamin D can be helpful to maintain adequate bone density in this group of patients. Kribbs (1992) reported that 83% of the women with postmenopausal osteoporosis taken daily 1000 mg calcium and multivitamin supplement with 400 IU of vitamin D over 2 years, maintained or increased their mandibular bone mass. In addition, Krall *et al* (2001) showed an association between calcium and vitamin D supplements and lower risk of tooth loss in elderly men and women.

There are a wide variety of risk factors implicated in the development of osteoporosis. In this study, the groups were matched for gender, age, menopausal state and BMI. However, other confounding factors including year since menopause, hormone replacement therapy for women, physical activity and calcium intake were not taken into account, which is the limitation of this study. The decrease in BMD in female patients did not reach to statistical significance in our study. While this maybe a reflection of the small sample size, it may be also due to the differences in other factors such as oestrogen levels in female patients.

In conclusion, the present study provides evidence suggesting that long-term inhaled corticosteroid treatment may impair bone metabolism leading to a considerable decrease in the mandibular BMD. Measurement of BMD of the mandible may be advised for patients receiving long-term corticosteroid treatment to estimate one of the risk factors for osteoporosis. However, it is difficult to draw a conclusion on the association of inhaled corticosteroids with tooth loss and periodontal status. Further studies using larger groups of populations are required to draw definitive conclusions on the relationship between health of the dentition and the mineral status of the jaws in COPD patients under long-term inhaled corticosteroid treatment.

References

Ainamo J, Barmes D, Beagrie G (1982). Development of the world health organization (WHO) community periodontal index of treatment needs (CPITN). *Int Dent J* **32:** 281–291.

Dubois EF, Roder E, Dekhuijzen PN *et al* (2002). Dual energy X-ray absorptiometry outcomes in male COPD patients after treatment with different glucocorticoid regimens. *Chest* **121:** 1456–1463.

Gennari C (1993). Differential effect of glucocorticoids on calcium absorption and bone mass. *Br J Rheumatol* **32:** 11–14.

GOLD Workshop Report (2003). www.goldcopd.com.

Hanania NA, Chapman KR, Sturtridge WC *et al* (1995). Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* **96:** 571–579.

Horner K, Devlin H, Alsop CW *et al* (1996). Mandibular bone mineral density as a predictor of skeletal osteoporosis. *Br J Radiol* **69:** 1019–1025.

Kerstjens HA, Postma DS, van Doormaal JJ *et al* (1994). Effects of short-term and long-term treatment with inhaled corticosteroids on bone metabolism in patients with airways obstruction. Dutch CNSLD Study Group. *Thorax* **49:** 652–656.

Klemetti E, Collin HL, Forss H *et al* (1994). Mineral status of skeleton and advanced periodontal disease. *J Clin Periodontol* **21:** 184–188.

Krall EA, Garcia RI, Dawson-Hughes B (1996). Increased risk of tooth loss is related to bone loss at the whole body, hip, and spine. *Calcif Tissue Int* **59:** 433–437.

Krall EA, Wehler C, Garcia RI *et al* (2001). Calcium and vitamin D supplements reduce tooth loss in the elderly. *Am J Med* **111:** 452–456.

Kribbs PJ (1990). Comparison of mandibular bone in normal and osteoporotic women. *J Prosthet Dent* **63:** 218–222.

Kribbs PJ (1992). Two-year changes in mandibular bone mass in an osteoporotic population. *J Prosthet Dent* **67:** 653–655.

Lipworth BJ (1999). Systemic adverse effects of inhaled corticosteroid therapy. *Arch Intern Med* **159:** 941–955.

Loe H, Silness J (1963). Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odontol Scand* **21:** 533–551.

Lundstrom A, Jendle J, Stenstrom B *et al* (2001). Periodontal conditions in 70-year-old women with osteoporosis. *Swed Dent J* **25:** 89–96.

Meeran K, Hattersley A, Burrin J *et al* (1995). Oral and inhaled corticosteroids reduce bone formation as shown by plasma osteocalcin levels. *Am J Respir Crit Care Med* **151:** 333–336.

National Institutes of Health, Osteoporosis and Related Diseases, National Resource Centre (2003). *Biochemical Markers of Bone Turnover*. www.osteo.org.

Olgaard K, Storm T, van Wowern N *et al* (1992). Glucocorticoid-induced osteoporosis in the lumbar spine, forearm, and mandible of nephrotic patients: a double-blind study on the high-dose, long-term effects of prednisone versus deflazacort. *Calcif Tissue Int* **50:** 490–497.

Ronderos M, Jacobs DR, Himes JH *et al* (2000). Association of periodontal disease with femoral bone mineral density and estrogen replacement therapy: cross-sectional evaluation of US adults from NHANES III. *J Clin Periodontol* **27:** 778–786.

Safkan B, Knuuttila M (1984). Corticosteroid therapy and periodontal disease. *J Clin Periodontol* **11:** 515–522.

Scannapieco FA, Ho AW (2001). Potential associations between chronic respiratory disease and periodontal disease: Analysis of National Health and Nutrition Examination Survey III. *J Periodontol* **72:** 50–56.

Silness J, Loe H (1964). Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. *Acta Odontol Scand* **22:** 121–135.

Sivri A, Coplu L (2001). Effect of the long-term use of inhaled corticosteroids on bone mineral density in asthmatic women. *Respirology* **6:** 131–134.

Southard TE, Southard KA, Krizan KE *et al* (2000). Mandibular bone density and fractal dimension in rabbits with induced osteoporosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **89:** 244–249.

Taguchi A, Suei Y, Ohtsuka M *et al* (1999). Relationship between bone mineral density and tooth loss in elderly Japanese women. *Dentomaxillofac Radiol* **28:** 219–223.

Wilson AM, Lipworth BJ (1999). 24 hour and fractionated profiles of adrenocortical activity in asthmatic patients receiving inhaled and intranasal corticosteroids. *Thorax* **54:** 20–26.

Wisniewski AF, Lewis SA, Green DJ (1997). Cross sectional investigation of the effects of inhaled corticosteroids on bone density and bone metabolism in patients with asthma. *Thorax* **52:** 853–860.

Wong CA, Walsh LJ, Smith CJ *et al* (2000). Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* **22:** 1399–1403.

von Wowern N, Klausen B, Olgaard K (1992). Steroid-induced mandibular bone loss in relation to marginal periodontal changes. *J Clin Periodontol* **19:** 182–186.

von Wowern N, Klausen B, Kollerup G (1994). Osteoporosis: a risk factor in periodontal disease. *J Periodontol* **65:** 1134–1138.