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Intestinal calcium absorption and parathyroid hormone secretion in asthmatic patients on prolonged oral or inhaled steroid treatment

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Intestinal calcium absorption on and parathyroid hormone secretion in asthmatic patients on prolonged oral or inhaled steroid treatment. M. Luengo, C. Picado, C. Piera, N. Guañabens, J.M. Montserrat, J. Rivera, J. Setoain.
ABSTRACT: A secondary hyperparathyroidism resulting from decreased intestinal calcium (Ca) absorption has been proposed as a contributory factor to glucocorticoid-induced osteoporosis. Inhaled steroids do not usually suppress adrenal gland function unless daily doses above 1,500 μg are used. A recent study, however, has shown a reduced total body calcium in patients on regular beclomethasone treatment. In theory, osteopenia in these patients could be due to a direct effect of inhaled steroids on bone or due to an impaired intestinal calcium absorption.

In this study, Ca absorption and parathyroid hormone (PTH) secretion were evaluated in three groups: 1) asthmatics on continuous oral and inhaled steroid treatment (11.3±4.4, range 5–33.5 mg·day^{-1} prednisone and 660±265, range 400–1,600 μg·day^{-1} beclomethasone, respectively); 2) asthmatics on regular beclomethasone therapy (585±210, range 400–1,200 μg·day^{-1}); and 3) healthy subjects. The prevalence of vertebral fractures was evaluated by a spinal X-ray.

No differences were found in either Ca absorption or PTH serum levels between asthmatics and healthy subjects (analysis of variance - ANOVA). Vertebral fractures were significantly more frequent in patients from group 1 (14 of 25) than in those from group 2 (2 or 25).

We conclude that both prolonged oral steroid treatment and inhaled steroids, at doses lower than 1,600 μg·day^{-1} do not cause Ca malabsorption, and that hyperparathyroidism does not contribute to osteoporosis in these patients.
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Although the pathogenesis of osteoporosis has not been fully elucidated it has been suggested that an impaired intestinal calcium (Ca) absorption may be responsible, at least in part, for this complication [1]. A state of hyperparathyroidism resulting from a decreased intestinal Ca absorption has been proposed as a possible contributory factor in steroid-induced osteoporosis. Increased parathyroid gland activity, as indicated by an elevated serum level of the patathyroid hormone (PTH) has been observed in patients treated with supraphysiological levels of steroids [2]. In contrast to oral steroids, inhaled steroids (beclomethasone and budesonide) are considered to be free of systemic adverse side-effects, if doses below 1,500 μg·day^{-1} are used. In a recent study, however, REID *et al.* [3] found that asthmatic patients on regular beclomethasone treatment showed a reduced total body calcium. This finding suggests that inhaled steroids, like oral steroids, may exert a deleterious effect on bones either by a direct action on bone metabolism or by interfering with intestinal calcium absorption. Since a high proportion of the aerosolized dose is deposited in the oropharynx and afterwards swallowed [4], it is also possible that the local anti-inflammatory effects of inhaled steroids may affect the gut mucosa and thereby Ca absorption.

The present study was designed to investigate the effects of proloned oral and inhaled steroid treatment on intestinal calcium absorption and PTH secretion in steroid-dependent asthmatics.

Materials and methods

Patients

Twenty five consecutive adult asthmatic patients on continuous beclomethasone treatment (585±210, range 400–1,200 μg·day^{-1}) were studied. Asthma was diagnosed when there was a history of shortness of breath, wheezing, and evidence of reversible airway

obstruction defined as an increase of at least 15% in forced expiratory volume in one second. Thirteen of these patients had never received short courses of oral steroids (SCOS), four had been treated with four SCOS during the last year, six with two SCOS and two with three, but none of them had ever been on prolonged oral steroid treatment. In our unit the usual policy for SCOS is to start with 30–40 mg of prednisone for two to three days, tapering off 5 mg every two days.

Twenty five, oral steroid-dependent asthmatics matched for sex and age (a difference within 3 yrs was accepted) with patients on beclomethasone were also included in the study. Patients on alternate-day steroid therapy were excluded. Each patient from this group was maintained at the lowest possible oral dose. Prednisone was the only oral corticosteroid used on a single-morning basis. In all patients, periodic attempts to discontinue the use of steroids had demonstrated that this was not feasible. Oral steroid tretment was evaluated taking into account length of treatment and average daily dose.

Twenty five healthy volunteers, matched by age (a difference within 3 yrs was accepted) and sex with the asthmatics, were also recruited for the study from the staff of our institution. The criteria for inclusion were current good health and absence of any treatment at the time of recruitment.

None of the subjects included in the study showed clinical symptoms or signs suggesting that they were suffering from a disease potentially responsible for osteoporosis. Subjects on medications known to cause bone-mineral alterations such as oestrogens, androgens, fluoride, vitamin D, heparin, diuretics and anticonvulsants were excluded.

Characteristics of the patients and healthy subjects are presented in table 1.

Intestinal calcium absorption and PTH serum levels

An intestinal calcium absorption test was performed by a single-isotope technique according to the Marshall and Nordin method [5]. After an overnight fast, the subject was given 5 μCi of ^{47}Ca orally in a solution of 20 mg of calcium chloride in 250 ml of distilled water. Plasma samples were taken at 60 min, and the fractional calcium absorption was calculated by non-linear curve fitting. Serum parathyroid hormone levels were measured by radio-immunoassay directed to the N-terminal fraction (PTH radio-immunoassay, Nichols Institute Diagnostics). Sensitivity of the method is 5 $pg \cdot ml^{-1}$ and the intra- and interassay variation is 4 and 7.3%, respectively. All studies were carried out when patients were on their usual medication or at least two weeks after the end of a short steroid course. The patients had taken the last dose of beclomethasone and oral steroid 12 and 24 h, respectively, prior to blood extraction. Blood samples were taken between 8 and 9 a.m.

Radiological study

Thoracic and lumbar spine X-ray in two projections were obtained from all asthmatic patients. A vertebral fracture was diagnosed when the anterior height of the vertebra was less than 75% of the posterior height (wedge fracture), and when the posterior height of the vertebra was less than the 85% of the posterior height of an adjacent vertebra (crush fracture) [6]. Radiological evaluation was carried out blind by an experienced observer.

Statistical analysis

Statistical analysis was performed using analysis of variance (ANOVA), Chi-squared test and Pearson's correlation when appropriate. A probability value of 0.05 was considered significant.

Results

Vertebral fractures

Fourteen patients on oral steroid treatment disclosed 51 fractures (40 wedge and 11 crush), whilst only 2 patients from the beclomethasone group (3 wedge and 2

Table 1. – Characteristics of patients

	Group I Oral steroid n=25	Group II Beclomethasone n=25	Group III Healthy subjects n=25
Sex ratio F/M	15/10	15/10	15/10
Age yrs	52 (12.6)	51 (11.4)	52 (13.5)
Postmenopausal yrs	5.7 (7.5)	6.9 (11.8)	5.9 (10.2)
Duration steroid treatment yrs	7.4 (5.5)	-	-
Beclomethasone $\mu g \cdot day^{-1}$	660 (262)	585 (210)	-
Duration inhaled steroid treatment yrs	6.7 (6.2)	6.7 (3.8)	-

All values are expressed as mean (SD).

Table 2. – Calcium absorption values and PTH serum levels

	Group I Oral steroid	Group II Inhaled steroid	Group III Healthy
Ca absorption	0.56 (0.24)	0.61 (0.23)	0.62 (0.23)
PTH pg·ml^{-1}	14.3 (3.9)	12.6 (4.1)	12.2 (4.8)

All values are expressed as mean (SD). Ca absorption expressed fractional Ca absorption at 60 min. PTH: parathyroid hormone.

crush) showed vertebral fractures (p=0.017). There were no correlations between either duration or dosage of oral steroid treatment with the number of vertebral fractures. None of the patients had been affected by fractures (legs, hips, *etc.*) other than vertebral fractures. Subclinical rib fractures, however, were not evaluated by a radiological study.

Intestinal Ca absorption and PTH serum levels

No differences were found in intestinal Ca absorption between asthmatics and healthy subjects (ANOVA) (table 2). There were no correlations between daily steroid doses and length of treatment with Ca absorption. Similary, there were no differences between fracture patients and those with normal spines with respect to Ca absorption. Nor were there differences in PTH values between patients and healthy subjects (table 2).

Discussion

The increased bone resorption seen in steroid-induced osteoporosis has generally been attributed to elevated PTH levels resulting from the inhibitory effects of steroids on intestinal Ca absorption [1]; our results do not support this suggestion. This discrepancy may be due to differences in steroid treament or in the methods used to study intestinal Ca absorption. For instance, when high steroid doses are administered for at least one week (more than 40 mg prednisoone-equivalent daily) a decreased intestinal Ca absorption is generally found [7, 8]. However, when steroids are given in lower doses or for shorter periods of time, little or no effect on Ca absorption has been observed [7, 9]. Variable effects have also been found with regard to PTH and corticosteroid treatment [2, 8, 9]. Again, differences in doses and length of treatment may account for these discrepancies. Prolonged treatment with doses 5–15 mg·day^{-1} is probably well-tolerated, and some kind of adaptation may exist to normalize intestinal Ca absorption. A similar phenomenon has been found in bone architecture using histomorphometric studies. A rapid loss of bone has been observed during the first 6 wks of steroid treatment but the rate of loss slows thereafter and can even be completely arrested [10].

Differences in the methodology employed to evaluate Ca absorption may also account for these discrepancies; for instance, with the radio-calcium absorption method used in this, only unidirectional Ca flux (Ca-influx) is measured. Braun *et al.* [11], however, have recently reported that steroids may increase intestinal Ca secretion (Ca-efflux). This phenomenon can only be detected when net Ca absorption is evaluated by subtracting faecal loss of Ca from oral Ca intake. These authors suggested that steroid treatment may cause an abnormal intestinal Ca absorption balance by increasing endogenous Ca secretion. In any case, if this abnormal balance did exist in our patients it was of little relevance since it did not cause a significant increase in PTH release. The pathogenesis of steroid-induced osteoporosis in asthmatic patients on long-term treatment with daily low doses of steroids is likely to be complex. Histomorphometric studies show that glucocorticoids suppress osteoblast function and increase bone resorption [12]; although this last finding has been linked to a possible hypersecretion of PTH our results and other studies suggest that secondary hyperparathyroidism does not play any role in steroid-related osteoporosis. It has been suggested that the accentuated bone resorption seen in bone biopsies from patients on prolonged steroid treatment might be the consequence of an increased sensitivity of bones (induced by steroids) to the resorbing action of PTH.

Our study shows that beclomethasone treatment has no effect on Ca absorption and PTH secretion. A direct effect of beclomethasone on bone architecture cannot be excluded by our patients on continuous inhaled aerosol treatment disclosed vertebral fractures. Whether this is a coincidental finding or perhaps related to short courses of steroids and beclomethasone treatment cannot be established from our study.

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Absorption intestinale du calcium et sécrétion d'hormone parathyroïdienne chez des patients asthmatiques sous traitement stéroïdien prolongé par voie orale ou par inhalation. M. Luengo, C. Picado, C. Piera, N. Guanabens, J.M. Montserrat, J. Rivera, J. Setoain.

RÉSUMÉ: L'on a suggéré, comme facteur contributif à l'ostéoporose induite par les gluco-corticoïdes, un hyperparathyroïdisme secondaire, résultant d'une diminution de la résorption intestinale du calcium. Habituellement, les stéroïdes par inhalation ne déprime pas la fonction de la suprarrénale à des doses égales ou inférieures à 1,500 µg. Dans une étude récente toutefois, l'on a démontre, chez les patients sous traitement régulier à la beclomethasone, une réduction du calcium total du corps. En théorie, chez ces patients, l'ostéopénie pourrait être due à une effet direct des stéroïdes inhalés sur l'os, ou à une absorption réduite du calcium par l'intestin.

Dans cette étude, l'absorption du calcium et la sécrétion d'hormone parathyroïdienne (PTH) ont été évaluées chez trois groupes de sujets: 1) asthmatiques sous traitement aux stéroïdes, continu par voie orale ou par inhalation (11.3±4.4 écart 5–33.5 mg·jour^{-1} de prednisone et 660±265, écart 400–1,600 µg de beclomethasone par jour, respectivement); 2) asthmatiques sous traitement régulier à la beclomethasone (585±210, écart 400–1,200 µg par jour); 3) sujets sains. La prévalence des fractures vertébrales a été évaluée par radiographie de la colonne.

L'on n'a trouvé aucune différence dans l'absorption du calcium ou dans les niveaux sériques de PTH entre les sujets asthmatiques et les sujets sains (ANOVA). Toutefois, les fractures vertébrales s'avèrent significativement plus fréquentes chez les patients du groupe 1 (14/25) que chez ceux de groupe 2 (2/25).

Nous concluons que, aussi bien les traitements prolongés par voie orale que par inhalation au moyen de stéroïdes, à des doses inférieures à 1,600 µg par jour, ne provoquent pas de malabsorption du calcium; l'hyperparathyroïdie ne contribue pas à l'ostéoporose chez ces patients.
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