

Effects of short term and long term treatment with inhaled corticosteroids on bone metabolism in patients with airways obstruction

Huib A M Kerstjens, Dirkje S Postma, Jasper J van Doormaal, Annie K van Zanten, Paul L P Brand, P N Richard Dekhuijzen, Gerard H Koëter, on behalf of the Dutch CNSLD Study Group

Abstract

Background - Recent reports have suggested short term changes in serum parameters of bone metabolism with inhaled corticosteroids. The relevance of these findings to the balance between bone formation and resorption during years of corticosteroid treatment remains uncertain.

Methods - Two novel markers of bone turnover were first compared with conventional markers in a pilot study and subsequently measured in a long term double blind study of inhaled corticosteroids. In study I 15 patients were newly started on at least 800 µg inhaled corticosteroids daily. At entry and after four weeks serum levels of alkaline phosphatase, osteocalcin, and PICP (procollagen type I carboxy terminal propeptide; a procollagen splice product) were measured as markers of bone formation, as well as the urinary hydroxyproline/creatinine ratio and serum levels of ICTP (type I collagen carboxy terminal telopeptide; a collagen degradation product) as markers of bone resorption. In study II 70 patients with airways obstruction received 800 µg beclomethasone daily in addition to terbutaline and 85 received bronchodilators only in a double blind fashion. Serum levels of PICP and ICTP were measured before and after 2.5 years of treatment.

Results - In study I a decrease in osteocalcin levels was accompanied by an increase in levels of PICP and a small and non-significant rise in alkaline phosphatase. There were no changes in hydroxyproline or ICTP. In study II no differences were found in serum levels of PICP between the treatment groups; an increase in serum ICTP was found in the group treated without inhaled corticosteroids compared with the group treated with inhaled corticosteroids.

Conclusions - No detrimental long term effect of inhaled corticosteroids was found with three conventional and two novel parameters of bone metabolism. The results indicate that long term changes in bone turnover during treatment with inhaled corticosteroids should not be deduced from short term studies with single serum parameters of bone metabolism, but well designed long term studies of, for example, bone densito-

metry should be awaited before quoting detrimental effects of inhaled corticosteroids on bone metabolism.

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Inhaled corticosteroids are currently administered to more patients with asthma and chronic obstructive pulmonary disease (COPD), at an earlier stage, and in higher dosages than previously.¹⁻³ Long term use of inhaled steroids has been shown to reduce exacerbations and hospital stay and to delay further deterioration of lung function.³ As far as current knowledge goes, however, this requires patients to take inhaled corticosteroids 2-4 times daily for many years. Although the short term direct adverse effects of inhaled corticosteroids seem to be acceptable, there is increasing discussion of possible adverse effects after years of usage.

One of the important adverse effects of oral corticosteroids is osteoporosis, eventually leading to fractures.⁴ A few studies on the effects of inhaled corticosteroids on bone turnover have been published.⁵⁻¹⁰ There are suggestions of growth deceleration in children⁶ and decreased bone formation in adults.⁷⁻¹⁰ To our knowledge, however, no controlled and randomised studies have been performed to investigate the long term (more than a few months) effects of inhaled corticosteroids on bone turnover in patients with asthma or COPD.

In the present study two novel serum markers of bone turnover were used to assess the effects of treatment with inhaled corticosteroids for 2.5 years on bone formation and resorption, respectively. The carboxy terminal propeptide of type I collagen (PICP) is split from procollagen during its transformation into collagen.¹¹ The latter constitutes 90% of the organic bone matrix. Elevated levels of PICP are thus directly associated with increased bone formation as determined by biopsies.^{12,13} Systemic corticosteroid treatment is associated with decreased levels of PICP.¹⁴ A novel serum marker of bone resorption was also employed, namely the carboxy terminal telopeptide of type I collagen, crosslinked via pyridinoline crosslinks (ICTP) and liberated during its degradation.¹⁵ Increases in serum ICTP concentrations are found in conditions of increased bone lysis.^{13,16} In a four week pilot study with inhaled corticosteroids these novel parameters were compared with serum levels of osteocalcin and alkaline phosphatase as

Department of
Pulmonology
H A M Kerstjens
D S Postma
P L P Brand
G H Koëter

Department of
Endocrinology
J J van Doormaal

Department of
Nuclear Medicine
A K van Zanten

University Hospital
Groningen,
Groningen, The
Netherlands

Department of
Pulmonology, St
Radboud Hospital,
Nijmegen, The
Netherlands
P N R Dekhuijzen

Reprint requests to:
Dr H A M Kerstjens,
Department of Pulmonary
Medicine, University
Hospital Groningen,
Oostersingel 59, 9713 EZ
Groningen, The
Netherlands.

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markers of bone formation, and with the urinary hydroxyproline/creatinine ratio as a marker of bone resorption.¹⁷

Methods

STUDY I

Fifteen patients (table 1) with airways obstruction (asthma and COPD) who had not received any corticosteroids in the previous three months were started on at least 800 µg inhaled corticosteroids daily (eight budesonide, seven beclomethasone). Before and after four weeks of treatment with inhaled corticosteroids serum levels of alkaline phosphatase, osteocalcin, PICP, and ICTP were measured, as well as the 24 hour urinary hydroxyproline/creatinine ratio. Informed consent of all patients was obtained.

STUDY II

Stored serum samples of a recently completed multicentre study of 274 patients with airways obstruction were used.³ Serum samples were drawn at the start and end of the study from 155 patients (table 1) who stayed on double blind medication for 2.5 years.³ All patients received a β_2 agonist (terbutaline 2000 µg daily), together with either an inhaled corticosteroid (beclomethasone 200 µg four times a day, n = 70) or an anticholinergic (ipratropium bromide 160 µg daily, n = 44), or a placebo (n = 41). Serum samples were never drawn within a month of a course of oral steroids. The study protocol was approved by the medical ethics committees of all participating centres; all patients gave written informed consent.

PICP and ICTP levels were measured in one batch with radioimmunoassay (RIA) kits from Orion Diagnostica, Espoo, Finland; these tests have an intra- and interassay variation of 3% and 5% for PICP,¹¹ and 6% and 8% for ICTP, respectively.¹⁵ Data on long term storage of PICP and ICTP are not yet available, but repeated freezing and thawing of serum samples can be applied with minor loss of activity.^{11,15} Blood drawn for osteocalcin measurements was immediately stored on ice until centrifuged and stored at -80°C. It was measured in one batch by RIA (Inctar Corporation, Stillwater, USA). Serum levels of alkaline phosphatase were measured with an automated sequential analyser (Technicon SMA), and urinary hydroxyproline was measured by high performance liquid chromatography and spectrophotometry.

Table 1 Patient characteristics in studies I and II

	Study I (n = 15)	Study II (n = 155)
M:F	7:8	101:54
Current smokers	7	59
Mean (SD) age (years)	44.1(19)	40.0(12)
Mean (SD) FEV ₁ (% predicted)	86.7(22)	65.5(16)
PC ₂₀ histamine (geometric mean)	10.2	0.29

FEV₁ = forced expiratory volume in one second; PC₂₀ = concentration of histamine causing a 20% fall in FEV₁ by the two minute tidal breathing method.³

DATA ANALYSIS

Because of non-normal distributions the data are presented as medians; non-parametric comparisons of medians were performed with Wilcoxon and Mann-Whitney U tests. The correlation coefficients in study I are parametric (Pearson's) as the variables tested were normally distributed.

Results

STUDY I

Osteocalcin levels decreased significantly within four weeks of commencing treatment with inhaled corticosteroids (table 2, fig 1). In contrast, PICP levels increased significantly, as did the ratio of PICP to ICTP. There were no significant changes in the urinary hydroxyproline/creatinine ratio, or in serum levels of alkaline phosphatase and ICTP. The changes in osteocalcin levels were significantly corre-

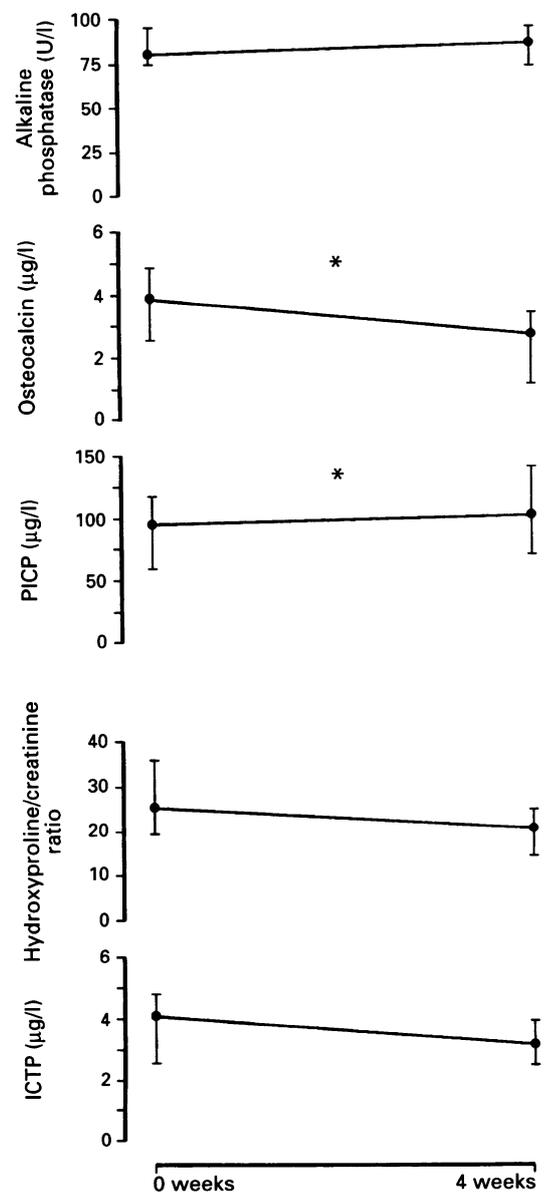


Figure 1 Study I: Short term changes in parameters of bone turnover during four weeks of treatment with inhaled corticosteroids. Medians \pm interquartile ranges. * $p < 0.05$ changes from start to end of study.

Table 2 Parameters of bone turnover before and after treatment with inhaled corticosteroids

	Reference value	Median	Interquartile range	Median	Interquartile range	p†
Study I:						
Alkaline phosphatase (U/l)	30–120	81	75–95	87	75–96	NS
Osteocalcin (µg/l)	1.8–6.6	3.9	2.5–4.9	2.7	1.1–3.5	0.04
PICP (µg/l)	F50–170, M38–202	96	60–119	103	72–142	0.03
Hydroxyproline/creatinine	10–33	25.2	20–36	20.5	15–25	NS
ICTP (µg/l)	1.8–5.0	4.1	2.6–4.8	3.2	2.5–4.0	NS
Study II:						
PICP (µg/l)		Start		2.5 years		p‡
ICS group	F50–170, M38–202	117	91–152	119	97–148	NS
No ICS group		107	83–139	106	95–124	
ICTP (µg/l)		Start		2.5 years		
ICS group	1.8–5.0	3.0	2.6–3.7	3.2	2.3–3.7	0.01
No ICS group		2.9	2.5–3.7	3.7	3.0–4.4	

PICP = carboxy terminal propeptide of procollagen type I; reference values from ref. 11; ICTP = carboxy terminal telopeptide region of type I collagen crosslinked via pyridinoline crosslinks; reference values from ref. 15; hydroxyproline/creatinine = hydroxyproline/creatinine ratio in 24 hour urine; ICS = inhaled corticosteroids; F = female, M = male; †p value for comparison between begin and end of four weeks of treatment with inhaled corticosteroids; ‡p value for comparison of the changes between treatment groups with 2.5 years of treatment; NS = non-significant ($p > 0.05$, two sided).

lated with changes in ICTP ($r = 0.79$, $p < 0.005$) but not with changes in PICP ($r = 0.14$, $p > 0.05$). No significant differences could be detected in changes in serum levels of osteocalcin, PICP, and ICTP between patients on budesonide ($n = 8$) or beclomethasone ($n = 7$), nor between patients on 800 µg ($n = 10$) and 1600 µg of inhaled corticosteroids ($n = 5$).

STUDY II

The parameters of bone formation were not significantly different between the two groups receiving only bronchodilators (terbutaline with ipratropium or with placebo) and are consequently pooled in the analyses presented. PICP levels remained unchanged after 2.5 years of treatment in both groups (table 2). ICTP levels rose slightly in the corticosteroid treated group and significantly in the non-corticosteroid treated group, the difference being significant ($p < 0.01$; table 2, fig 2). PICP

and ICTP levels at the start were significantly lower in older patients (Spearman's $\rho = -0.15$ and -0.32 respectively; $p < 0.05$), but changes in PICP and ICTP levels were not age dependent. When all 20 women over 40 years of age were omitted thereby excluding possible influences of changes in oestrogen status, the same results were obtained.

Discussion

No clear evidence of a detrimental effect of inhaled corticosteroids on bone metabolism was found when several parameters of bone metabolism were used in a short term open study and a long term randomised controlled clinical trial.

We have confirmed the results of Pouw and others that osteocalcin levels decrease with short term use of inhaled corticosteroids.^{8,9} The other markers of bone formation, however, increased non-significantly (alkaline phosphatase) and significantly (PICP).

The exact relation of osteocalcin to bone metabolism has not yet been elucidated.¹⁸ Although osteocalcin is generally presented as a marker of bone formation since it is released from the osteoblast, it is also to some extent released from the bone matrix during bone resorption.¹⁹ Moreover, osteocalcin is chemotactic for osteoclastic cells and could play a part in the induction of bone resorption and bone turnover.^{20,21} In postmenopausal women higher osteocalcin levels are associated with an increased risk of hip fractures.²² These findings relate well to the much closer correlation of changes in osteocalcin levels to ICTP levels (bone resorption) than to PICP levels (bone formation) found in our study. A histomorphometric study has suggested that PICP is a more specific indicator of bone formation than osteocalcin.¹² These observations taken together suggest that osteocalcin might not be a valid marker of bone formation alone, but also of bone resorption, and it might therefore be more useful in metabolic bone disease than in assessing changes with inhaled corticosteroids.

A significant increase in levels of PICP was detected with four weeks of treatment with

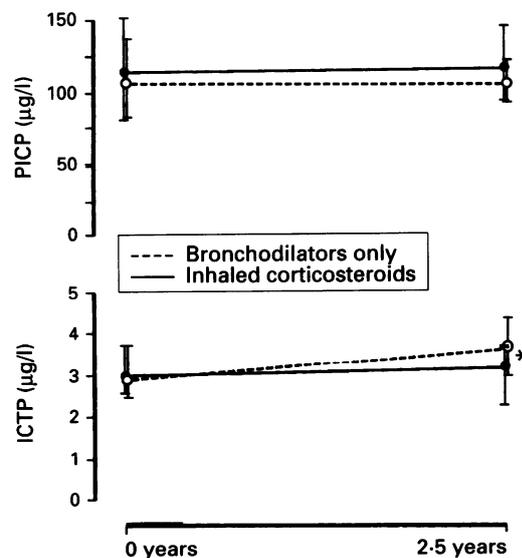


Figure 2 Study II: Long term changes in parameters of bone turnover during 2.5 years of double blind therapy. Medians \pm interquartile ranges. * $p < 0.05$ differences in changes from start to end of study between the two treatment groups.

inhaled corticosteroids compared with a small and non-significant rise after 2.5 years of treatment. This suggests that the short term changes found in serum parameters of bone metabolism may become balanced after a longer period of time. A similar difference between short term and long term effects on bone metabolism has been seen in children where short term reduction in linear growth rate as measured with knemometry (0.36 mm/week) cannot be extrapolated to a reduction of 18.6 cm after 10 years of treatment with inhaled corticosteroids.⁶

Next to a decrease in bone formation, increased bone resorption has also been suggested as a side effect of inhaled corticosteroids.⁷ In our short term study, however, no such evidence was found. If increased bone resorption occurs an increase in the urinary hydroxyproline/creatinine ratio would be expected, but instead a non-significant fall was found, accompanied by a non-significant fall in ICTP, a collagen degradation product. With 2.5 years of treatment with inhaled corticosteroids no change in ICTP levels was found, but with 2.5 years of treatment with bronchodilators an unexpected rise in ICTP was detected. Several explanations have been considered. It is unlikely that a change of activity of the prestudy serum samples that had been stored for 2.5 years explains the relative rise in ICTP, since all serum samples were stored identically for the same period of time; the relative difference between the groups treated with and without inhaled corticosteroids is therefore still meaningful. It is also unlikely that the assay has been disturbed by the medication still present in the serum samples; the rise in ICTP was equally present in both groups that received bronchodilators only (terbutaline with or without ipratropium) but not in the group that received terbutaline and beclomethasone. A more likely explanation is that the level of physical activity was lower in the group without corticosteroids than in the group treated for 2.5 years with inhaled corticosteroids. Immobilisation leads to increased bone resorption with the reverse occurring after subsequent mobilisation.²³ After 2.5 years of corticosteroid treatment PICP levels had not changed significantly, signifying no effect on bone formation.

The absence of differences between budesonide and beclomethasone in effects on bone metabolism, and also between 800 and 1600 µg of inhaled corticosteroid in study I, should be interpreted with care as patients were not randomised to the different inhaled corticosteroids and groups were small.

Results of several studies suggest that short term treatment with inhaled corticosteroids reduces bone formation and perhaps increases bone resorption in adults.⁷⁻¹⁰ However, these studies were performed in healthy volunteers,⁷⁻⁹ were retrospective¹⁰ or uncontrolled,^{7,9,10} and all were performed with high doses of corticosteroids.⁷⁻¹⁰ Our results are different from the above mentioned studies and were performed in patients with conventional doses of inhaled corticosteroids. More-

over, we followed patients in a double blind manner for 2.5 years on inhaled corticosteroids.

Overall, our results indicate that long term changes in bone turnover during treatment with inhaled corticosteroids should not be deduced from short term studies with single serum parameters of bone metabolism. Using three conventional and two novel parameters of bone metabolism no clear detrimental effect on bone formation or resorption was found, except for a fall in osteocalcin levels. The exact place of osteocalcin as a parameter of bone formation in patients with inhaled corticosteroids, however, is uncertain.

Our results are in line with the clinical impression that the number of fractures has not increased since inhaled corticosteroids were introduced 20 years ago. It is clear that randomised controlled studies which use more specific measures of bone status (such as bone densitometry or preferably number of fractures) and which evaluate inhaled corticosteroid effects over periods of at least several years, are needed.

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The Dutch CNSLD study group consists of a steering committee (K F Kerrebijn, Ph H Quanjer and H J Sluiter (deceased)), of members from the Departments of Pulmonology of the University Hospital of Amsterdam (E M Pouw, D F M E Schoonbrood, C M Roos, H M Jansen), Groningen (P L P Brand, A de Gooyer, H A M Kerstjens, D S Postma, Th W van der Mark, H J Sluiter†, G H Koëter), Leiden (P M de Jong, P J Sterk, A M J Wever, J H Dijkman), Nijmegen (P N R Dekhuijzen, H T M Folgering, C L A van Herwaarden), Rotterdam (S E Overbeek, J M Bogaard, C Hilvering) and Utrecht (S J Gans, H J J Mengelers, B A H A van der Bruggen-Bogaarts, J Kreukniet), Departments of Pediatric Pulmonology at the Sophia Children's Hospital, Rotterdam (E E M van der Essen-Zandvliet, K F Kerrebijn), The Juliana Children's Hospital, The Hague (E J Duiverman, J M Kouwenberg, J E Prinsen), University Hospital of Groningen (H J Waalkens, J Gerritsen, K Knol), Department of Allergology, University Hospital of Groningen (J G R de Monchy), Department of General Practice, Leiden University (F W Dekker), Department of Psychiatry, University Hospital Leiden (A A Kaptein), and Department of Physiology, Leiden University (P J F M Merkus, Ph H Quanjer). Scientific counsel: S J Pocock, M D Hughes (London, UK), E R Bleeker, D A Meyers (Baltimore, USA).

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