# Adverse Effects of Corticosteroid Therapy for COPD*

## A Critical Review

*Charlene E. McEvoy, MD, MPH; and Dennis E. Niewoehner, MD, FCCP*

**Inhaled and systemic corticosteroids are commonly prescribed for the treatment of COPD. Despite their frequent use, there is insufficient evidence regarding efficacy of steroid therapy in COPD. While awaiting the results of more definitive prospective trials, the clinician must evaluate whether the benefits of such therapy outweigh the potential for adverse events. This is particularly pertinent in the population of patients with COPD who generally are older, less active, and have significant tobacco use histories, all of which may place them at greater risk for adverse effects. In this review, we examine the current scientific evidence supporting the many purported adverse systemic effects associated with the use of corticosteroids in the treatment of COPD.** ***(CHEST 1997; 111:732-43)***

**Key words:** adverse effects; chronic obstructive pulmonary disease; corticosteroids

**Abbreviations:** ACTH=corticotropin; HPA=hypothalamic-pituitary-adrenal; PSC=posterior subcapsular cataract

COPD remains one of the leading causes of disability and death in developed countries. In addition to bronchodilators, oxygen, and antibiotics, many physicians prescribe inhaled and systemic corticosteroids. Large doses of systemic corticosteroids are now a standard therapy for the inpatient and outpatient therapy of COPD exacerbations, and lower doses may be administered for extended periods in some "steroid-dependent" patients. Additionally, many patients with symptomatic COPD receive inhaled corticosteroids. High doses of systemic corticosteroids given short term cause a small increase in the mean $FEV_1$ of patients with stable COPD.[1] They may have a similar effect in COPD exacerbations, but the evidence is not as strong.[2-4] To our knowledge, no large studies have assessed longer-term, clinical outcomes of systemic corticosteroid treatment for either stable or acute COPD.[5] Despite their widespread use, there is also insufficient evidence to judge whether inhaled corticosteroids are effective in COPD.[6-10] The central issue is whether the benefits of such therapies outweigh the cost and the potential for serious adverse effects. This review will critically examine the existing evidence concerning the potential risks of inhaled and systemic corticosteroid use in the treatment of COPD.

It is believed that corticosteroid therapy may cause adrenal insufficiency, osteoporosis, peptic ulcer disease, cataract formation, dermal thinning, hypertension, diabetes, infection, psychosis, and hyperadrenocorticism.[11-13] Not all of these complications have been conclusively linked to corticosteroid therapy, and where a reasonably strong association has been established, the incidence and severity are usually not known. Different diseases may place patients at greater or lesser risk of corticosteroid complications, so that wherever possible, assessments of risk should be made on a disease-specific basis. Important distinguishing characteristics of COPD include the following: (1) patients tend to be elderly; (2) nearly all have a significant cigarette smoking history; (3) those with severe disease have a limited life expectancy; and (4) most receive relatively low cumulative doses of corticosteroids. A large prospective randomized clinical trial of long duration is best suited to establish the true incidence of corticosteroid-associated adverse clinical events. We know of no such study that exists for the specific population of patients with COPD, and a study of this type may not be feasible. As a result, expected side effects must be extracted from case reports, cross-sectional surveys, retrospective analyses, meta-analyses, and case-control studies evaluating the adverse effects of corticosteroid treatment in patients both with respiratory disease and with other medical conditions.

*From the Pulmonary Section, Veterans Affairs Medical Center and University of Minnesota, Minneapolis.
Supported by the Minnesota Medical Foundation, University of Minnesota School of Public Health, and NIH Training Grant HL07741.
Manuscript received June 7, 1996; revision accepted August 9.

It is generally believed that inhaled corticosteroids have less potential for serious adverse effects than do systemic corticosteroids. The most common adverse effects of inhaled corticosteroids are local reactions caused by their deposition in the oropharynx.[14-17] These include oropharyngeal candidiasis, dysphonia, wheezing, and cough. Positive throat cultures for Candida species are commonly found in adult asthmatics taking inhaled corticosteroids, and clinically significant oropharyngeal candidiasis occurs in approximately 9 to 13% of those patients with a positive culture.[14,17] Dysphonia is a more frequent side effect, occurring in up to 50% of patients.[15] Cough and wheezing also occur following inhalation of some corticosteroid preparations, and this may be caused by propellant additives rather than the corticosteroid itself.[16] These topical phenomena can generally be managed by simple measures such as spacer devices, mouth rinsing, and reduction in dosage. This subject has been extensively reviewed and we will comment on inhaled corticosteroids only with regards to their potential for systemic adverse effects.

## Adrenal Suppression

Long-term administration of oral corticosteroids clearly affects hypothalamic-pituitary-adrenal (HPA) function, but there is less certainty concerning the magnitude of the effect and its persistence once corticosteroid therapy is discontinued. Miyamoto and associates[18] found that corticotropin (ACTH)-stimulated cortisol responses were suppressed to some extent in all 48 asthmatics who had been treated long term with oral corticosteroids. Cortisol responses showed some recovery by 1 month with return to normal by 1 year in the five patients who discontinued the drug treatment. In contrast, Tuft and colleagues[19] found abnormal metapyrone test results in only three of 15 oral corticosteroid-treated asthmatics. More recently, Schlaghecke and coinvestigators[20] evaluated HPA axis responsiveness by the corticotrophin-releasing hormone stimulation test in 279 patients treated with daily corticosteroids for various chronic diseases and in 50 normal control subjects. Of the subjects who had been taking oral corticosteroids, 37% had a normal response, 48% had a blunted response, and 15% had no response to corticotrophin-releasing hormone administration. They also found no association between the plasma cortisol response and the dose or duration of corticosteroid therapy.

A number of studies have also addressed changes in HPA axis function with inhaled corticosteroid use. Comparisons between asthmatics, primarily children and young adults, and normal control subjects revealed no significant effects on HPA function from relatively low doses of inhaled corticosteroids (400 to 800 μg/d of beclomethasone).[21,22] However, Brown and associates[21] found that of 78 adult asthmatics taking ≥1,500 μg inhaled corticosteroid daily, 20.5% showed some evidence of HPA suppression. Risk factors associated with this suppression were a previous requirement for long-term systemic corticosteroids and a longer duration of high-dose inhaled therapy.

Corticosteroid-induced adrenal insufficiency that becomes clinically apparent is probably uncommon. Axelrod[23] in a 1976 review found "few well documented cases" of adrenocortical insufficiency following corticosteroid therapy. Most corticosteroid-dependent asthmatics with blunted responses to ACTH can safely undergo major surgery, even if preoperative corticosteroid therapy is withheld.[24] Deaths from adrenal insufficiency crisis in corticosteroid-dependent patients appear to be rare.[13] There are sporadic case reports of adrenal insufficiency after withdrawal of inhaled corticosteroid therapy, but only one of these occurred in an adult.[25] Thus, it is reasonable to suspect that some degree of HPA suppression frequently accompanies long-term corticosteroid therapy in COPD. The existing literature suggests that serious clinical events resulting from adrenal suppression are uncommon.

## Effects on Bone

Cushing[26] first reported skeletal decalcification as a characteristic feature of adrenal hyperplasia secondary to ACTH-producing pituitary tumors. Subsequent work has confirmed that hypercorticism has deleterious effects on bone metabolism, but the pathogenic mechanisms remain only partly characterized. Corticosteroids appear to target areas with high trabecular bone content such as the ribs and vertebrae.[27] Studies consistently show that corticosteroids cause a decrease in calcium absorption, but effects on vitamin D metabolism, on bone resorption and formation, and on renal calcium and phosphorus excretion may also be important.[28-30]

Osteoporosis is arguably the most feared complication of long-term corticosteroid administration, but the magnitude of the clinical impact in patients with COPD is difficult to judge for a number of reasons. Most importantly, most studies evaluating the severity and potential mechanisms of corticosteroid-induced bone loss in patients with COPD do not include appropriate disease-matched control subjects. That is, COPD patients treated with corticosteroids are not compared to equivalent patients not treated with corticosteroids. This is particularly

important because COPD and its principal identified cause, cigarette smoking, may by themselves be significant risk factors in the development of osteoporosis.[31,32] Patients taking corticosteroids also tend to be severely limited by their disease, and inactivity may pose another osteoporosis risk factor.[33]

It is believed that circulating levels of osteocalcin indirectly reflect new bone formation. Meeran and colleagues[28] measured osteocalcin levels in 34 adult patients requiring oral prednisone for the treatment of either asthma or COPD. Subjects were matched for age, sex, and $FEV_1$ with control subjects who had either asthma or COPD but who had not taken long-term oral corticosteroids. Osteocalcin levels were significantly reduced in those patients requiring corticosteroids on a long-term basis as compared to control subjects (6.3±0.1 ng/mL vs 8.6±0.5 ng/mL; $p<0.01$). They also prospectively evaluated the effects of both oral and inhaled corticosteroids on osteocalcin levels in normal volunteers. Both oral prednisone (15 mg qd for 1 week) and inhaled beclomethasone (500 μg bid for 1 week) caused highly significant reductions in serum osteocalcin levels (11.8±1.1 ng/mL to 6.9±0.8 ng/mL and 11.6±0.6 ng/mL to 9.6±0.6 ng/mL, respectively). Though the study design does not allow a direct comparison, osteocalcin levels were substantially lower in asthma/COPD patients who had taken no corticosteroids as compared to the baseline values of normal volunteers who participated in the second part of the study. This poses the interesting question as to whether the underlying lung diseases by themselves might suppress new bone formation.

Two recent studies evaluating the osteocalcin levels in patients with chronic illnesses support this hypothesis. Praet and colleagues[34] compared serum osteocalcin levels in 44 men, ages 39 to 80 years, with a diagnosis of chronic bronchitis to 90 healthy age-matched control subjects. The investigators reported significantly lower osteocalcin levels in patients both treated and not treated with systemic corticosteroids when compared to healthy control subjects. Hall and associates[35] measured osteocalcin levels in 106 postmenopausal women with rheumatoid arthritis. Compared to control subjects, patients with rheumatoid arthritis had significantly lower osteocalcin levels regardless of whether they were treated with corticosteroids. Osteocalcin levels tended to be lower in those patients treated with corticosteroids compared to those not treated, but the difference was not significant.

To our knowledge, there are no published randomized trials or prospective, long-term cohort studies that were designed to specifically evaluate corticosteroid-induced bone loss in patients with respiratory disease. Laan and associates[36] prospectively evaluated the effect of short-term, low-dose prednisone therapy (10 mg/d for 12 weeks, then tapered and discontinued by week 20) and placebo on bone mass in 40 patients with active rheumatoid arthritis. They measured bone mineral density of the lumbar spine by dual-energy, quantitative CT. Trabecular bone mineral density in the prednisone-treated group decreased by 8.2% ($p<0.001$) from baseline and by 9.5% compared to placebo ($p<0.003$). Cortical bone mineral density did not change significantly in either group. This study was well executed, but it was not designed to determine whether the decrease in trabecular bone mineral density was predictive of clinically important fractures. Dual-energy, quantitative CT is very sensitive to changes in trabecular bone density, but it lacks the precision of other available methods. Also, to our knowledge, prospective studies to determine whether changes in bone density as measured by quantitative CT are predictive of clinically important fractures have not been done.

Osteoporosis has been evaluated as an adverse effect in some trials in which oral corticosteroids were administered for the treatment of any medical disorder. Conn and Poynard[37] performed a meta-analysis of 93 double-blinded, randomized, controlled trials, and of the 8,700 patients included in the analysis, 1,435 (placebo=722; corticosteroid=713) patients had been evaluated for the development of osteoporosis. Osteoporosis was reported seven times more frequently in patients receiving oral corticosteroids, but this difference did not reach statistical significance. The authors accepted as valid the investigator's diagnosis of osteoporosis. We are not provided with information regarding the length of study follow-up, the duration or dose of corticosteroid treatment, or the criteria of osteoporosis diagnosis.

Several observational and cross-sectional studies have reported an association between long-term corticosteroid use and lower bone mineral density. Bikle and associates[30] measured lumbar spine bone mineral density, serum 1,25-dihydroxyvitamin D and parathormone levels, and urine calcium excretion in 36 men with a diagnosis of COPD. Twenty-two of these patients had been treated with oral prednisone for 1 to 16 years. The groups were well matched for age, though they differed significantly in their $FEV_1$. The authors found significantly lower bone mineral density measurements in prednisone-treated patients as compared to those who received no systemic corticosteroids. They also found significantly higher urine calcium and serum 1,25-dihydroxyvitamin D levels, but not parathormone levels, in the corticosteroid treatment group. Of interest, they found a highly significant correlation between bone mineral density and the patient's $FEV_1$, even after adjustment for corticosteroid use. Bone mineral density was lowest in those patients with the most severe ventilatory dysfunction. Since the average

$FEV_1$ differed significantly between their two study groups, it is not clear whether the measured differences in bone mineral density were due to corticosteroid use or to the differences in severity of the underlying disease.

Reid and associates,[38] in a cross-sectional analysis of 35 patients receiving corticosteroids for the treatment of either asthma or connective tissue disease, found the bone mineral density of the spine to be significantly lower than normal standards. However, no comparison was made with disease-matched control subjects to determine if factors other than corticosteroid use may have influenced the outcome measurements. Reid and Heap[39] attempted to address this issue in a second cross-sectional analysis of bone mass in asthmatics. In this study, asthmatics using oral or inhaled corticosteroids were compared to both asthmatic and normal control subjects. They found that asthmatics using oral or inhaled corticosteroids on a long-term basis had a significant decrease in bone mass when compared to either of the control groups. Unfortunately, the authors did not perform an age-adjusted analysis which is essential since the asthmatic control subjects who used neither inhaled nor oral corticosteroids were much younger (mean age, 37.9 years) than either the oral corticosteroid (mean age, 54.1 years) or the inhaled corticosteroid group (mean age, 55.6 years). Thus, the actual contribution of oral corticosteroids to decreased bone density in these investigations remains uncertain.

In a similar study, Brandli and coworkers[40] studied 70 patients who had been treated with oral corticosteroids for at least 6 months and compared bone mineral density measurements of the spine and hip to age-matched, but not disease-matched control subjects. Forty-five of these patients carried a diagnosis of either asthma or COPD. Compared to the age-matched control subjects, patients with a pulmonary diagnosis had decreased bone mineral density both of the hip (11.5% less than control subjects) and of the spine (12.9% less than control subjects). However, there was no significant correlation between current dose, cumulative dose, or duration of corticosteroid therapy with bone density. A dose-response gradient would support the contention that corticosteroids induce bone loss,[41] but this study did not establish such a relationship.[40] In addition, the failure to incorporate appropriate disease-matched control subjects limits conclusions one might draw from the results.

The importance of disease-matched control subjects is illustrated by the previously cited study by Praet and colleagues.[34] In addition to measuring parameters of bone metabolism, the authors measured bone density of the proximal radius by single photon absorptiometry and of the spine by dual photon absorptiometry in 19 men with COPD requiring prednisone daily for at least 1 year and in 25 men with COPD using bronchodilator therapy only. The two groups were similar in age, weight, height, smoking habits, and $FEV_1$%. The authors did not include the mean daily dose of prednisone in their steroid treatment group but they did provide the cumulative dose (median, 11.4 g; range, 4.8 to 28.5 g). Compared to normal white male volunteers, they found significantly lower spinal bone density in both groups with COPD and a lower proximal radial bone density only in the steroid-treated group. Their evidence suggests that men with COPD are at risk for osteoporosis regardless of steroid usage. However, as the authors point out, the clinical consequences of this observation in terms of increased fracture incidence needs to be explored with a large prospective study.

Adinoff and Hollister[42] examined the association between corticosteroid use and prevalent vertebral fractures in patients with asthma. In the first study of 128 consecutively discharged asthmatic patients treated long term with prednisone, 11% had vertebral and/or rib fractures; no fractures were documented in the control group of 54 asthmatics who had not required long-term administration of corticosteroids. Data on potential confounding variables such as age, sex, and pulmonary function were not provided. Since corticosteroids are usually prescribed for patients with the more severe lung dysfunction, it is possible that factors related to disease severity, rather than the corticosteroids themselves, led to the difference in fracture prevalence between the two groups. Furthermore, the authors did not use a standardized method in assessing vertebral fractures.

In a second study, the same authors matched 19 asthmatic subjects who received long-term continuous corticosteroid therapy and 11 asthmatics who received intermittent corticosteroids for age, severity of disease, sex, and serum theophylline levels. Eight of the 19 subjects with continuous corticosteroid use, or 42%, showed evidence of osteoporosis by a history of spontaneous rib or vertebral fractures, as compared to 0% in the intermittent therapy group. It is not clear how these particular subjects were selected for study. This point is important because the prevalence of fractures is so much higher in this group of long-term prednisone-treated patients (42%) as compared to a similar group in their first study (11%). This unexplained difference in the two asthmatic populations raises questions as to whether the samples were representative.

Several investigations suggest that inhaled corticosteroids may depress bone formation or increase

bone resorption, potentially leading to osteoporosis. Ali and associates[43] found a significant increase in the urinary hydroxyproline:creatinine ratio, a biochemical marker of bone resorption, and a fall in serum alkaline phosphatase activity, a marker of bone mineralization, in healthy male volunteers after 28 days treatment with 2,000 μg/d of inhaled beclomethasone dipropionate. Pouw and colleagues[44] reported that serum osteocalcin, a protein produced exclusively by bone-forming cells, decreased significantly in eight healthy volunteers treated with the same dose of inhaled beclomethasone after only 1 week of use.

Kerstjens and associates[45] evaluated longer-term effects of inhaled corticosteroids on bone turnover in a randomized, multicenter, placebo-controlled trial of 274 patients with a diagnosis of either asthma or COPD. All patients received an inhaled β-adrenergic agonist and they also randomly received a fixed dose of inhaled beclomethasone (800 μg/d) vs either an inhaled anticholinergic or a placebo. They found no significant group difference in numerous indirect measures of bone turnover over a 30-month period. They did not directly measure bone mineral density in these patients and the study was not designed to detect clinically significant osteoporosis.

Ip and coworkers[46] conducted a small cross-sectional survey of bone mineral density in 30 asthmatics using inhaled corticosteroids. Women using an average of 1,100 μg/d (beclomethasone dipropionate and/or budesonide) for at least 3 months (mean duration, 40±43 months) had a significantly lower bone mineral density measured at the lumbar spine and hip compared to healthy age- and sex-matched control subjects. The effects in men did not reach statistical significance, but the numbers were small and the study population was young (32±9 years).

In a similar study, Packe and associates[47] compared bone density in three groups of asthmatics. Group 1 included 17 asthmatics who had never taken inhaled or systemic corticosteroids. Group 2 included 20 asthmatics taking 1,000 to 2,000 μg of beclomethasone dipropionate daily for at least a year along with intermittent courses of system corticosteroids. Group 3 included 20 patients taking daily high-dose inhaled corticosteroids (beclomethasone dipropionate, 1,000 to 2,000 μg/d) and prednisolone at a median dose of 7 mg/d. Osteocalcin, serum alkaline phosphatase, serum calcium, and a marker of bone resorption, urinary pyridinoline, were measured in all subjects. The groups were well matched for age but differed significantly in their $FEV_1$, median values being 3.34 L, 2.62 L, and 1.86 L, for groups 1, 2 and 3, respectively. They found that bone density was significantly lower in group 2 and 3 when compared to the corticosteroid-free group 1, but they did not find significant group differences for any of the biochemical markers. Unfortunately, they did not include an adjustment for the differences in $FEV_1$ in their analysis, and thus it is not clear whether the observed differences were confounded by disease severity.

These data support the general idea that corticosteroid administration is associated with some deleterious effects on bone metabolism. However, the magnitude and clinical significance of these effects are not known. Prospective studies that include disease-matched control subjects are needed to clarify the effects of systemic and inhaled corticosteroids on bone in both men and women.

## GI Effects

Three meta-analyses of placebo-controlled, randomized, double-blind clinical trials performed in the past 20 years examined the association of systemic corticosteroid use with the development of peptic ulcer disease. To our knowledge, no studies examined this issue exclusively in patients with COPD. Conn and Blitzer[48] analyzed 26 such trials and found no association between corticosteroid use and peptic ulcer disease. In a subsequent meta-analysis of 71 randomized, controlled trials, Messer and associates[49] reported a twofold increase in the relative risk of developing peptic ulcer disease from taking systemic corticosteroids or ACTH. More recently, Conn and Poynard[37] contradicted that finding in a meta-analysis of 93 randomized, double-blind, controlled trials. They found no significant association between systemic corticosteroid use and peptic ulcer disease, and they attributed their differing results to "conceptual, selectional and executional flaws" in the Messer et al[49] analysis. Conn and Poynard[37] reanalyzed the data of Messer et al and were unable to demonstrate a statistically significant association between corticosteroid use and the occurrence of peptic ulcers.

A case-control study by Piper and colleagues[50] support the conclusions of Conn and Poynard. In their study of elderly Medicaid patients (1,415 cases; 7,063 control subjects), they found an increased risk of developing peptic ulcer disease only in current users of corticosteroids who were also taking nonsteroidal anti-inflammatory drugs (relative risk, 4.4; confidence interval, 2.0 to 9.7). There was no increased risk associated with corticosteroid use alone. They suggested that earlier studies purporting to show an association between the use of corticosteroids and peptic ulcer disease may have been confounded by the concomitant use of nonsteroidal anti-inflammatory drugs.

A cohort analysis of 19,880 patients by Carson and associates[51] found that the incidence of peptic ulcer disease in corticosteroid-treated patients without a history of upper GI bleeding was only 2.8 cases per 10,000 person-months. The incidence increased significantly if patients had a history of GI bleeding (15.9 cases per 10,000 person-months) or current use of anticoagulants (23.0 cases per 10,000 person-months).

In summary, evidence does not support an association between systemic corticosteroid use and the development of peptic ulcer disease. Whether patients with COPD and an associated history of tobacco use history are at greater risk for peptic ulcer disease may warrant further investigation. To our knowledge, there are no published studies linking inhaled corticosteroids with dyspepsia or peptic ulcer disease.

### Psychiatric Effects

The best prospective study supporting an association between corticosteroid therapy and psychiatric disturbances is the Boston Collaborative Drug Surveillance Program.[52] Of 676 patients treated with corticosteroids, including 149 with COPD, 3.1% developed acute psychosis or inappropriate euphoria. The relationship was significantly dose dependent with acute psychiatric reactions occurring in 1.3% of the 463 patients receiving <40 mg prednisone daily, 4.6% of 175 patients receiving 41 to 80 mg of prednisone daily, and 18.4% of 38 patients receiving >80 mg prednisone daily. The authors found no disease-specific effect at any of the dosing intervals. Reduction or controlled withdrawal of the corticosteroid therapy resulted in resolution of symptoms in all cases.

A retrospective case series analysis by Smyllie and Connolly[12] is consistent with those results in showing that adverse psychiatric events are relatively uncommon with lower doses of systemic corticosteroids. As compared to their control subjects, they found no increase in reported psychiatric complications in 550 COPD patients treated with a mean daily dose of 10 mg prednisone.

Conn and Poynard[37] performed meta-analysis on 7,210 patients enrolled in randomized, placebo-controlled trials, for whom data were available regarding adverse psychiatric reactions. They found a significant association between the development of psychiatric side effects and the use of oral corticosteroids ($p<0.02$).[37] Ten of the 3,321 subjects in the placebo groups and 19 of the 3,889 subjects in the treatment groups, who were receiving a mean daily dose of 35 mg prednisone, experienced reportable adverse psychiatric events.

Evidence of systemic behavioral effects following use of inhaled corticosteroids is supported by only a few case reports.[53-55] Insomnia, depression, mania, euphoria, nightmares, and somnolence have been reported in young asthmatics using inhaled corticosteroids, with behavior returning to baseline following discontinuation of treatment with the inhaler. Adverse psychiatric or behavioral effects from inhaled corticosteroids have either not been evaluated or reported in prospective clinical trials.

### Infectious Complications

Corticosteroids in sufficient doses impair antibody production and exert a variety of other immunosuppressive effects.[56-59] Therefore, it is logical to suspect that systemic administration of corticosteroids might place the patient at increased risk of serious infection.

The strongest evidence for increased risk of infection from corticosteroids is a meta-analysis of 71 controlled clinical trials in which patients were randomized to treatment of their illness with corticosteroids or placebo.[60] When all diagnostic groups were included in the analysis, Stuck and associates[60] found a significant risk of lethal and nonlethal infections in patients receiving systemic corticosteroids (relative risk, 1.6; 95% CI; confidence interval, 1.3 to 1.9). This association was dose dependent with no increased risk found in patients receiving <10 mg prednisone a day or a cumulative dose <700 mg. When underlying disease was considered, they detected no significant increase in the incidence of infection in those patients with a pulmonary diagnosis (n=364). The greatest risk of infection was found in those patients with renal and neurologic diseases. This may be explained partly by the larger mean daily dose of prednisone given to the neurologic disease group (90 mg) as compared to the pulmonary disease group (30 mg), but it does not explain the increased risk in the renal group (26 mg). However, the duration of corticosteroid therapy was much longer in the renal disease group (mean=421 days) than in the pulmonary disease group (mean=14 days), and this might explain the greater risk of infection seen in the former.

Conn and Poynard,[37] in their meta-analysis, reported that patients treated with corticosteroids developed bacterial sepsis 1½ times more frequently than did those subjects receiving placebo. Analysis of infectious risk in this study was not done on a disease/diagnostic category basis, and whether bacterial sepsis was more prevalent in corticosteroid-treated patients with COPD is not stated.

Increased risk of infection was not found in three

analyses of long-term corticosteroid treatment in patients with asthma or COPD.[12,13,19] Most patients included in these studies took relatively low doses of prednisone for extended periods. Smyllie and Connolly[12] identified no cases of *mycobacterium tuberculosis,* one case of pulmonary fungal infection, and three cases of acute bacterial infection in the 550 patients evaluated retrospectively. Most of these patients (n=353) took a mean daily prednisone dose of ≤10 mg for at least 2 years, and only 31 patients took daily doses >20 mg. Lieberman and colleagues[13] performed a cross-sectional analysis of 50 asthmatics taking a mean daily prednisone dose of 9.4 mg for at least 2 years. The authors found no association between corticosteroid use and the reactivation of tuberculosis. The number of patients with a known positive purified protein derivative, which would place them at higher risk of reactivation, was not reported. Tuft and coworkers[19] found no cases of serious infection in 20 asthmatics treated with low doses of prednisone for periods up to 15 years.

Aside from the occasional case report,[61] to our knowledge, there are no published reports claiming that inhaled corticosteroids cause an increased risk of serious systemic infection. However, the available evidence consists largely of short-term studies, not all of which were controlled.[14,62,63]

## Glucose Intolerance

It is well established that corticosteroids may cause glucose intolerance, and it is believed that the mechanisms relate both to increased hepatic glucose production and to decreased peripheral glucose utilization.[64] The available literature is reasonably consistent in showing that long-term systemic corticosteroid treatment is associated with a greater risk of developing symptomatic diabetes mellitus.

Smyllie and Connolly,[12] in their retrospective review of corticosteroid therapy in respiratory disease patients, found a significant increase in the development of diabetes during the first 3 months of therapy (nine of 550 patients in the treatment group vs two of 499 in control subjects; p=0.012). The meta-analysis by Conn and Poynard[37] found that diabetes was reported four times more frequently in the corticosteroid treatment group compared to control subjects. Lieberman and associates[13] reported a 28% prevalence of glucose intolerance in 50 asthmatics treated with systemic corticosteroids for at least 2 years. They compared this to the reported prevalence of diabetes in the general population (approximately 4 to 5%) which was not age- or disease-matched.

There is little evidence to support clinically relevant changes in carbohydrate and lipid metabolism in patients receiving inhaled corticosteroids. Two studies, one in normal subjects and one in children with asthma, demonstrated mild corticosteroid-induced insulin resistance, as reflected by increases in serum insulin, lactate, and pyruvate levels.[65,66] Minor increases in cholesterol and in high-density lipoprotein levels were detected in another study.[67] However, both healthy nondiabetics and diet-controlled adult diabetics showed normal glucose tolerance and lipid profiles while taking inhaled beclomethasone dipropionate in doses ranging from 1,000 to 2,000 μg/d.[68] Kiviranta and Turpeinen[69] reported an improvement in glucose intolerance in 15 poorly controlled asthmatics after the initiation of inhaled corticosteroid therapy. This effect was attributed to a reduction in stress reactions induced by poorly controlled asthma. To our knowledge, the effects of inhaled corticosteroids on glucose and lipid metabolism in the older COPD population have not been studied.

## Myopathy

Muscle weakness associated with systemic corticosteroid administration was first described in the 1950s.[70] Animal and human biopsy studies demonstrate atrophy in the type IIb-fast twitch fibers in subjects receiving corticosteroids.[71-74]

Clinical evidence of significant myopathy associated with systemic corticosteroid use is supported primarily by case reports.[75,76] One case-control study by Bowyer and colleagues[76] in asthmatics demonstrated that 50% of the patients taking >40 mg/d of prednisone and 22% of those taking <40 mg/d of prednisone showed evidence of hip flexor weakness on formal muscle testing. The control subjects in this study were sedentary, age- and sex-matched, nonasthmatic volunteers. No comparisons were made with asthmatics not receiving corticosteroids, so it is unclear whether decreased muscle strength was due to corticosteroids or to the underlying disease.

Two studies compared respiratory muscle strength in asthmatics who had taken mean doses of 8 to 12 mg prednisone for several years with asthmatics who had not taken systemic corticosteroids.[77,78] Neither study found any significant differences in muscle strength between the two groups. The mean daily doses of prednisone in these two study groups, 8.0 and 11.9 mg, were substantially lower than in the study by Bowyer and his associates.[76]

Zanotti and colleagues[79] compared respiratory muscle strength in 12 systemic corticosteroid-treated patients with COPD (mean dose=12.5 mg prednisone equivalents; duration 4 to 18 months) to sex-,

age-, and $FEV_1$-matched control subjects who had never used corticosteroids. They also found no significant differences between the two groups.

Systemic corticosteroids are clearly capable of causing histologic abnormalities in skeletal muscle, and at higher doses they may cause significant muscle weakness. Available evidence does not suggest that long-term, low-dose systemic corticosteroid therapy is associated with significant muscle weakness, but larger studies may be required to detect the effect.

## Cutaneous Effects

Changes of the skin, including dermal thinning, easy bruisability, striae, moon facies, buffalo humps, and acne are the most frequently reported adverse effect of systemic corticosteroids. Moon facies has been reported in 13% of patients taking low-dose corticosteroids (≤12 mg) for at least 60 days and up to 66% of those taking the drug for >5 years.[15] Easy bruisability was reported in nearly 50% of corticosteroid-treated patients vs only 11% in the noncorticosteroid-treated asthmatic control subjects.[13] In the meta-analysis of Conn and Poynard,[37] cosmetic side effects, including moon face, buffalo hump, truncal obesity, acne, and hirsutism, were reported four times more frequently in the corticosteroid-treated patients as compared to the placebo-treated control subjects ($p<0.001$).

As with oral corticosteroids, inhaled corticosteroids may be associated with significant dermal thinning and purpura. In a cross-sectional study of patients receiving treatment for pulmonary diseases, Capewell and associates[80] reported a significant reduction in skin thickness in patients using high-dose inhaled corticosteroids (beclomethasone dipropionate, 1,000 to 2,250 μg/d) for either asthma or chronic bronchitis when compared to age-matched control subjects. Purpura was present in 48% of those patients receiving high-dose inhalation therapy. In a survey of 202 patients with asthma or COPD, Mak and colleagues[81] reported easy bruising as the most frequent symptom associated with inhaled corticosteroids, occurring in nearly 50% of the patients. The risk of bruising increased with age, dose, and duration of inhaled corticosteroid therapy.

## Cardiovascular Effects

Hypertension is the most commonly reported cardiovascular side effect of corticosteroid therapy. The mechanism by which corticosteroids might raise BP is not clearly defined, but it may be related to mineralocorticoid-induced increases in plasma volume.[82] Whether oral corticosteroids actually lead to an increased incidence of hypertension in patients with COPD is unknown.

Jackson and associates[83] retrospectively evaluated the rise in BP in 129 patients with asthma and in 66 patients with rheumatoid arthritis. When adjusted for age, mean daily prednisone doses of 6.7 mg and 8.4 mg in the asthma and rheumatoid arthritis groups, respectively, were not associated with the development of hypertension. Conversely, Lieberman and colleagues[13] reported a 40% prevalence of hypertension in 50 corticosteroid-dependent asthmatics compared to 18% in disease-, age-, and sex-matched control subjects. All data were collected retrospectively with no mention of baseline BP prior to initiation of corticosteroid use.

Conn and Poynard[37] found support for an association between systemic corticosteroid therapy and hypertension in their meta-analysis. In the studies included in their analysis, hypertension was reported four to five times more frequently in the corticosteroid-treated patients compared to placebo-treated control subjects. Their analysis does not make clear whether all studies used a uniform case definition of hypertension or whether the methods for measuring BP were consistent. Prospective, randomized, double-blind studies, which include baseline BP measurements prior to the initiation of either treatment or placebo, are necessary to eliminate the bias introduced by chance differences in baseline characteristics.

Possible effects of inhaled corticosteroids on the cardiovascular system have, to our knowledge, not have investigated.

## Ocular Effects

Black and associates[84] first reported the association of posterior subcapsular cataracts (PSC) with long-term corticosteroid use in 1960. In their evaluation of 47 patients with rheumatoid arthritis treated with corticosteroids, 17 developed PSC. Subsequent case series and cross-sectional analyses, primarily in the pediatric population, have supported this association.[85-89] However there is no consensus as to the dosage or duration of therapy that results in the development of PSC. Assessment of corticosteroid use and PSC in adult patients with respiratory disease has yielded inconsistent results.

Smyllie and Connolly[12] reported no eye complications in their series of 550 patients taking corticosteroids for respiratory disease. Lieberman and coworkers,[13] in their case-control review of 50 corticosteroid-treated asthmatics, detected cata-

racts in only two patients in the treatment group, both of whom were older than 50 years of age. In contrast, Urban and Collier[90] combined the results of nine surveys to evaluate the prevalence of PSC in a total of 343 asthmatics treated with systemic corticosteroids. The prevalence of PSC averaged 9% (range, 0 to 54%) and was influenced by the daily dose, cumulative dose, duration of corticosteroid use, as well as age and ethnicity.[90] Toogood and associates[91] found a 27% prevalence of PSC in 48 adult asthmatics taking on average of 1.3 mg of oral prednisone per day. Multiple-logistic regression analysis indicated that the current daily dose of prednisone was the strongest predictor for the presence of a PSC.[91]

Most data supporting a positive relationship between inhaled corticosteroids and PSC formation are anecdotal.[92-94] In the previously cited cross-sectional study of 48 adult asthmatics, Toogood and colleagues[91] found no association between the development of PSC and a history of long-term inhaled corticosteroid therapy or its dose and duration.

## Conclusions

It is evident from the foregoing discussion that the adverse effects of corticosteroid treatment for COPD are not clearly appreciated. We believe that such studies should be conducted on a disease-specific basis, because there are a number of unique considerations relating to the population with COPD. The history of heavy tobacco abuse and the disease itself may represent major confounding variables when attempting to assess possible adverse effects of corticosteroid therapy on bone and other organ systems. The limited life expectancy of patients with severe COPD reduces concern about some of the possible long-term adverse treatment consequences. Certain associations between corticosteroid therapy and adverse events do exist. However, based on "diagnostic tests for causation,"[95] the evidence does not prove that exogenous corticosteroids cause a substantial increase in morbidity or mortality in COPD. This may be due to the paucity of studies using a powerful research design, the failure to consistently establish a dose-response relationship, and the inconsistency of findings from study to study.

We believe that the available evidence supports the following conclusions about corticosteroid therapy in COPD.

(1) Inhaled corticosteroids are not known to be harmful, aside from mild cosmetic (cutaneous) and upper airway effects, but adequate long-term studies are not available.

(2) Suppression of HPA function occurs in some patients treated with systemic corticosteroids, but the magnitude of the effect and its duration are not predictable. The frequency of adverse clinical events due to HPA suppression is not known, but the number is probably very small.

(3) Use of systemic corticosteroids is associated with lower bone density, especially at trabecular sites. However, it is impossible to judge the magnitude of this effect, or, most importantly, whether it is clinically significant. Corticosteroid therapy may increase rib and vertebral fracture rates among patients with respiratory disease, but existing studies are flawed by failure to control for disease severity. To our knowledge, no studies have addressed the question as to whether rib and vertebral fractures contribute significantly to overall morbidity in patients with COPD. Well-designed, controlled prospective studies are needed to clarify the effects of corticosteroids on bone in both men and women. These studies should include the COPD population who have the additional risk factors for developing osteoporosis, including older age, inactivity level, and tobacco abuse.

(4) Available evidence does not support an association between systemic corticosteroid therapy and the development of peptic ulcer disease. Different meta-analyses have reached different conclusions concerning the risk of upper GI bleeding from systemic corticosteroids. Heavy tobacco use in patients with COPD might place such patients at greater risk of peptic ulcer disease, and further analysis of this patient group might be warranted. To our knowledge, there are no published investigations linking inhaled corticosteroids with dyspepsia or peptic ulcer disease.

(5) The literature indicates that systemic corticosteroids are strongly associated with some adverse psychiatric events. These effects appear to be dose dependent, but estimates of absolute risk vary widely. The incidence in patients with COPD is not known.

(6) Systemic corticosteroids are associated with a modest increased risk for lethal and nonlethal infections. This risk is likely dose dependent, and it is probably very small in patients who take low doses, even for extended periods. The actual risk imparted to a patient with COPD has not been adequately evaluated.

(7) Systemic corticosteroid therapy is associated with a significant increase in the number of newly diagnosed cases of diabetes mellitus. It is not known to what extent corticosteroid-induced diabetes contributes to overall morbidity and mortality in patients with COPD.

(8) Systemic corticosteroid therapy may be associ-

ated with a myopathy, but the supporting evidence consists of case reports and studies lacking adequate control subjects. Patients with respiratory disease taking low doses of corticosteroids do not appear to have significant impairment of respiratory muscle function. Additional studies are needed to clarify the role of low-dose systemic corticosteroid therapy on the development of clinically significant myopathy. Whether inhaled corticosteroids produce histologic changes in skeletal muscle or are associated with myopathy is unknown.

(9) Low doses of systemic and high doses of inhaled corticosteroids frequently are associated with dermal thinning, easy bruisability, and other skin abnormalities.

(10) Systemic steroid therapy may be associated with an increased incidence of hypertension, but the evidence in not conclusive.

(11) Case reports suggest that systemic corticosteroids may play a role in the development of PSCs in children. The evidence with regards to adults with respiratory disease is inconclusive.

## References


1 Callahan C, Dittus R, Katz B. Oral corticosteroid therapy for patients with stable chronic obstructive pulmonary disease: a meta-analysis. Ann Intern Med 1991; 114:216-23

2 Albert R, Martin T, Lewis S. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. Ann Intern Med 1980; 92: 753-58

3 Emerman CL, Connors AF, Lukens TW, et al. A randomized controlled trial of methylprednisolone in the emergency treatment of acute exacerbations of COPD. Chest 1989; 95:563-67

4 Rostom A, Mink S, Hebert PC, et al. The long-term efficacy of methylprednisolone in the emergency treatment of acute exacerbations of COPD. Chest 1994; 106(suppl):161S

5 Niewoehner D, Erbland M. Systemic corticosteroids in COPD—an unresolved clinical dilemma. Chest 1996; 110: 867-69

6 Watson A, Lim TK, Joyce H, et al. Failure of inhaled corticosteroids to modify bronchoconstrictor or bronchodilator responsiveness in middle-aged smokers with mild airflow obstruction. Chest 1992; 101:350-55

7 Weir D, Gove R, Robertson A, et al. Corticosteroid trials in non-asthmatic chronic airflow obstruction: a comparison of oral prednisolone and inhaled beclomethasone dipropionate. Thorax 1990; 45:112-17

8 Kerstjens H, Brand P, Hughes M, et al. A comparison of bronchodilator therapy with and without inhaled corticosteroid therapy for obstructive airways disease. N Engl J Med 1992; 327:1413-19

9 Engel T, Heinig J, Modsen O, et al. A trial of inhaled budesonide on airway responsiveness in smokers with chronic bronchitis. Eur Respir J 1989; 2:935-39

10 Auffarth B, Postma D, Monchy JD, et al. Effects of inhaled budesonide on spirometric values, reversibility, airway responsiveness and cough threshold in smokers with chronic obstructive lung disease. Thorax 1991; 46:372-77

11 David D, Grieco M, Cushman P Jr. Adrenal glucocorticoids after 20 years: a review of their clinically relevant consequences. J Chron Dis 1970; 22:637-711

12 Smyllie H, Connolly C. Incidence of serious complications of corticosteroid therapy in respiratory disease. Thorax 1968; 23:571-81

13 Lieberman P, Patterson R, Kunske R. Complications of long-term steroid therapy for asthma. J Allergy Clin Immunol 1972; 49:329-36

14 Toogood J, Jennings B, Greenway R, et al. Candidiasis and dysphonia complicating beclomethasone treatment of asthma. J Allergy Clin Immunology 1980; 2:145-53

15 Williams A, Baghat M, Stableforth D, et al. Dysphonia caused by inhaled steroids: recognition of a characteristic laryngeal abnormality. Thorax 1983; 38:813-21

16 Shim C, Williams MH Jr. Cough and wheezing from beclomethasone aerosol. Chest 1987; 91:207-09

17 Toogood J, Jennings B, Baskerville J, et al. Dosing regimen of budesonide and occurrence of oropharyngeal complications. Eur J Respir Dis 1984; 65:35-44

18 Miyamoto T, Yoshida T, Osawa N, et al. Adrenal response and side reactions after long-term corticosteroid therapy in bronchial asthma. Ann Allergy 1972; 30:587-94

19 Tuft L, Marks A, Channick B. Long-term corticosteroid therapy in chronic intractable asthmatic patients. Ann Allergy 1971; 29:287-93

20 Schlaghecke R, Kornely E, Santen R, et al. The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone. N Engl J Med 1992; 326:226-30

21 Brown P, Blundell G, Greening A, et al. Hypothalamo-pituitary-adrenal axis suppression in asthmatics inhaling high dose corticosteroids. Respir Med 1991; 85:501-10

22 Ninan T, Reid I, Carter P, et al. Effects of high doses of inhaled corticosteroids on adrenal function in children with severe persistent asthma. Thorax 1993; 48:599-602

23 Axelrod L. Glucocorticoid therapy. Medicine 1976; 55:39-65

24 Kehlet H, Binder C. Adrenocortical function and clinical course during and after surgery in unsupplemented glucocorticoid-treated patients. Brit J Anaesth 1973; 45:1043-48

25 Wong J, Black P. Acute adrenal insufficiency associated with high dose inhaled steroids. BMJ 1992; 304:1415

26 Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations. Bull Johns Hopkins Hosp 1932; 50:137-95

27 Seeman E, Wagner H, Offord K, et al. Differential effects of endocrine dysfunction on the axial and appendicular skeleton. J Clin Invest 1982; 69:1302-09

28 Meeran K, Hattersley A, Burrin J, et al. Oral and inhaled corticosteroids reduce bone formation as shown by plasma osteocalcin levels. Am J Respir Crit Care Med 1995; 151: 333-36

29 Hahn T, Halstead L, Teitelbaum S, et al. Altered mineral metabolism in glucocorticoid induced osteopenia. J Clin Invest 1979; 64:655-65

30 Bikle D, Halloran B, Fong L, et al. Elevated 1,25-dihydroxyvitamin D levels in patients with chronic obstructive pulmonary disease treated with prednisone. J Clin Endocrinol Metab 1993; 76:456-61

31 Seeman E, Melton LM III, O'Fallon W, et al. Risk factors for spinal osteoporosis in men. Am J Med 1983; 75:977

32 Daniell H. Osteoporosis of the slender smoker: vertebral compression fractures and loss of metacarpal cortex in relation to postmenopausal cigarette smoking and lack of obesity. Arch Intern Med 1976; 136:298

33 Sinaki M. Exercise and physical therapy. In: Riggs B, Melton LM III, eds. Osteoporosis: etiology, diagnosis. New York: Raven Press, 1988; 457-69

34 Praet J, Peretz A, Rozenberg S, et al. Risk of osteoporosis in men with chronic bronchitis. Osteoporosis Int 1992; 2:257-61
35 Hall G, Spector T, Delmas P. Markers of bone metabolism in postmenopausal women with rheumatoid arthritis. Arthritis Rheum 1995; 38:902-06
36 Laan RFJM, van Riel PLCM, van de Putte LBA, et al. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. Ann Intern Med 1993; 119:963-68
37 Conn H, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med 1994; 236:619-32
38 Reid D, Nicoll J, Smith M, et al. Corticosteroids and bone mass in asthma: comparisons with rheumatoid arthritis and polymyalgia rheumatica. BMJ 1986; 293:1463-66
39 Reid I, Heap S. Determinants of vertebral mineral density in patients receiving long-term glucocorticoid therapy. Arch Intern Med 1990; 150:2545-48
40 Brandli D, Golde G, Greenwald M, et al. Glucocorticoid-induced osteoporosis: a cross-sectional study. Steroids 1991; 56:518-23
41 Guyatt G, Webber C, Mewa A, et al. Determining causation—a case study: adrenocorticosteroids and osteoporosis. J Chron Dis 1984; 37:343-52
42 Adinoff A, Hollister J. Steroid-induced fractures and bone loss in patients with asthma. N Engl J Med 1983; 309:265-68
43 Ali N, Capewell S, Ward M. Bone turnover during high dose inhaled corticosteroid treatment. Thorax 1991; 46:160-64
44 Pouw E, Prummel M, Oosting H, et al. Beclomethasone inhalation decreases serum osteocalcin concentrations. BMJ 1991; 302:627-28
45 Kerstjens HAM, Postma DS, van Doormaal JJ, et al. Effects of short term and long term treatment with inhaled corticosteroids on bone metabolism in patients with airways obstruction. Thorax 1994; 49:652-56
46 Ip M, Lam K, Yam L, et al. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. Chest 1994; 105:1722-27
47 Packe G, Douglas J, McDonald A, et al. Bone density in asthmatic patients taking high dose inhaled beclomethasone dipropionate and intermittent systemic corticosteroids. Thorax 1992; 47:414-17
48 Conn H, Blitzer B. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976; 294:473-79
49 Messer J, Reitman D, Sacks H, et al. Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med 1983; 309:21-4
50 Piper J, Ray W, Daugherty J, et al. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991; 114:735-40
51 Carson J, Strom B, Schinnar R, et al. The low risk of upper gastrointestinal bleeding in patients dispensed corticosteroids. Am J Med 1991; 91:223-27
52 Program TBCDS. Acute adverse reactions in prednisone in relation to dosage. Clin Pharmacol Ther 1972; 13:694-98
53 Connett G, Lenney W. Inhaled budesonide and behavioral disturbances. Lancet 1991; 228:634-35
54 Meysboom R. Budesonide and psychotic side effects. Ann Intern Med 1988; 109:683
55 Lewis L, Cochrane G. Psychosis in child inhaling budesonide. Lancet 1983; 2:634
56 Cupps T, Fauci A. Corticosteroid mediated immunoregulation in man. Immunol Rev 1982; 65:133-55
57 Frey B, Walker C, Frey FJ, et al. Pharmacokinetics and pharmacodynamics of three different prednisone prodrugs: effect on circulation lymphocyte subsets and function. J Immunol 1984; 133:2479-87
58 Skerrett S, Niederman M, Fein A. Respiratory infections and acute lung injury in systemic illness. Clin Chest Med 1989; 10:469-502
59 Klaustermeyer WB, Gianos ME, Kurohara ML, et al. IgG subclass deficiency associated with corticosteroids in obstructive lung disease. Chest 1992; 102:1137-42
60 Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis 1989; 11:954-63
61 Blaiss M, Herrod H, Crawford L, et al. Beclomethasone dipropionate aerosol: hematologic and immunologic effects. Ann Allergy 1982; 48:210-14
62 Horton DJ, Spector SL. Clinical pulmonary tuberculosis in an asthmatic patient using a steroid aerosol. Chest 1977; 71: 540-42
63 Frank A, Dash C. Inhaled beclomethasone dipropionate in acute infections of the respiratory tract. Respiration 1985; 48:122-26
64 Olefsky J, Kimmerling G. Effects of glucocorticoids on carbohydrate metabolism. Am J Med Sci 1976; 271:202-10
65 Kruszynska Y, Greenstone M, Home P, et al. Effect of high dose inhaled beclomethasone dipropionate on carbohydrate and lipid metabolism in normal subjects. Thorax 1987; 42: 881-84
66 Turpeinen M, Sorva R, Juntunen-Backman K. Changes in carbohydrate and lipid metabolism in children with asthma inhaling budesonide. J Allergy Clin Immunol 1991; 88:384-89
67 Fancourt G, Ebden P, McNally P. The effects of high dose (2,000 micrograms/day) inhaled beclomethasone dipropionate (Becloforte) on glucose tolerance in diet controlled elderly diabetic subjects. Eur Respir J 1988; 1(suppl 2):196s
68 Ebden P, McNally P, Samanta A, et al. The effects of high dose inhaled beclomethasone dipropionate on glucose and lipid profiles in normal and diet controlled diabetic subjects. Respir Med 1989; 83:289-91
69 Kiviranta K, Turpeinen M. Effect of 8 months of inhaled beclomethasone dipropionate and budesonide on carbohydrate metabolism in adults with asthma. Thorax 1993; 48: 974-78
70 Perkoff G, Silber R, Tyler F, et al. Studies in disorders of muscle: XII. Myopathy due to the administration of therapeutic amounts of 17-hydrocorticosteroids. Am J Med 1959; 26:891-98
71 Ruff R. Endocrine myopathies. In: Engel A, Banke B, eds. Myology. New York: McGraw-Hill, 1986; 1871-1906
72 Wilcox P, Hards J, Bockhold K, et al. Pathologic changes and contractile properties of the diaphragm in corticosteroid myopathy in hamsters: comparison to peripheral muscle. Am J Respir Cell Mol Biol 1989; 1:191-98
73 Askari A, Vignos P, Moskowitz R. Steroid myopathy in connective tissue disease. Am J Med 1976; 61:485-92
74 Smith B. Histological and histochemical changes in the muscles of rabbits given the corticosteroid triamcinolone. Neurology 1964; 14:857-63
75 Decramer M, Stas K. Corticosteroid-induced myopathy involving respiratory muscles in patients with chronic obstructive pulmonary disease or asthma. Am Rev Respir Dis 1992; 146:800-02
76 Bowyer S, LaMothe M, Hollister J. Steroid myopathy: incidence and detection in a population with asthma. J Allergy Clin Immunol 1985; 76:234-42
77 Mak V, Bugler J, Spiro S. Sternomastoid muscle fatigue and twitch maximum relaxation rate in patients with steroid-dependent asthma. Thorax 1993; 48:979-84
78 Picado C, Fiz J, Montserrat J, et al. Respiratory and skeletal muscle function in steroid-dependent bronchial asthma. Am Rev Respir Dis 1990; 141:14-20

79 Zanotti E, Corsico R, Rampulla C, et al. Effect of long-term therapy with oral steroid on respiratory muscle function and ventilatory drive. Monaldi Arch Chest Dis 1993; 48:16-22
80 Capewell S, Reynolds S, Shuttleworth D, et al. Purpura and dermal thinning associated with high dose inhaled corticosteroids. BMJ 1990; 300:1548-51
81 Mak V, Melchor R, Spiro S. Easy bruising as a side-effect of inhaled corticosteroids. Eur Respir J 1992; 5:1068-74
82 Whitworth J. Mechanisms of glucocorticoid-induced hypertension. Kidney Int 1987; 31:1213-24
83 Jackson S, Beevers D, Myers K. Does long-term low-dose corticosteroid therapy cause hypertension? Clin Sci 1981; 61:381-83s
84 Black R, Oglesby R, von Sallmann L, et al. Posterior subcapsular cataracts induced by corticosteroids in patients with rheumatoid arthritis. JAMA 1960; 174:166-71
85 Castrow F. Atopic cataracts versus steroid cataracts. J Am Acad Dermatol 1981; 5:64-6
86 David D, Berkowitz J. Ocular effects of topical and systemic corticosteroids. Lancet 1969; 1:149-51
87 Giles C, Mason G, Duff I, et al. The association of cataract formation and systemic corticosteroid therapy. JAMA 1962; 182:719-22
88 Bihari M, Grossman B. Posterior subcapsular cataracts related to long-term corticosteroid treatment in children. Am J Dis Child 1968; 116:604-08
89 Crews S. Posterior subcapsular lens opacities in patients on long-term corticosteroid therapy. BMJ 1963; 53:1644
90 Urban R Jr, Collier E. Corticosteroid-induced cataracts. Surv Ophthalmol 1986; 31:102-10
91 Toogood J, Markov A, Baskerville J, et al. Association of ocular cataracts with inhaled and oral steroid therapy during long-term treatment of asthma. J Allergy Clin Immunol 1993; 91:571-79
92 Karim A, Thompson G, Jacob T. Steroid aerosols and cataract formation. BMJ 1989; 299:918
93 Fraunfelder F, Meyer S. Posterior subcapsular cataracts associated with nasal or inhalational corticosteroids. Am J Ophthalmol 1990; 109:489-90
94 Allen M, Ray S, Leitch A, et al. Steroid aerosols and cataract formation. BMJ 1989; 299:432-33
95 Hill A. The environment and disease: association or causation? Proc R Soc Med 1965; 58:295-300