Declining Bone Mass in Men With Chronic Pulmonary Disease*

Contribution of Glucocorticoid Treatment, Body Mass Index, and Gonadal Function

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Background: Men with chronic lung disease (CLD) are at risk for osteoporosis, but the relative contributions of their chronic pulmonary disease, glucocorticoid therapy, and other factors toward loss of bone has not been established. Understanding the relative importance of these factors would assist in selecting patients for bone densitometry screening and in policy decisions regarding Medicare reimbursement.

Objective: To identify patients with CLD who are most likely to benefit from bone densitometry screening based on clinical and biochemical measures.

Design: Cross-sectional medical survey.

Patients: Patients with CLD who were treated with either oral, inhaled, or no glucocorticoid therapy. A control group without lung disease was recruited from the same clinic population.

Measurements: Dual-energy X-ray absorptiometry was obtained for each group, and the association between bone mass and clinical variables, glucocorticoid use, gonadal hormones, and biochemical markers of bone metabolism was determined.

Results: Osteoporosis (a T score < −2.5 at the hip or spine) was five times as likely in patients with CLD as in control subjects. Although the prevalence of osteoporosis was higher (ninefold) after chronic glucocorticoid therapy, patients with CLD who had never been treated with glucocorticoids had a substantial (fourfold) risk of osteoporosis. Chronic inhaled glucocorticoid therapy offered no protection from bone loss compared to treatment with oral glucocorticoids. Of the clinical and biochemical measures that were obtained, bone mass was weakly correlated with body mass index (BMI), serum estradiol-17β, and N-telopeptide, but not with testosterone, alkaline phosphatase, bone-specific alkaline phosphatase, or osteocalcin.

Conclusion: Patients with CLD should be considered for bone densitometry screening regardless of glucocorticoid use. Those patients with a low BMI and/or decreased serum estradiol-17β comprise a subgroup with increased risk for osteoporosis. (CHEST 1999; 116:1616–1624)

Key words: COPD; densitometry; fracture; male; osteoporosis

Abbreviations: ANOVA = analysis of variance; BCE = bone collagen equivalents; BMD = bone mineral density; BMI = body mass index; Cr = creatinine; CI = confidence interval; DEXA = dual-energy X-ray absorptiometry; OSA = obstructive sleep apnea; WHO = World Health Organization

Recent epidemiologic data suggest that the relative risk of vertebral fracture in men is doubled by chronic illness.1 For men with chronic lung disease (CLD), osteoporosis is a serious health problem associated with pain, loss of independence, and increased mortality.2,3 In addition, thoracic vertebral fractures impair ventilation in CLD. It has been estimated that each vertebral compression fracture causes a 10% decrement of FVC in normal subjects; therefore, the effect of osteoporosis on pulmonary function in CLD must be substantial.4

Although much has been learned about the factors that contribute to bone loss, most of this information has been derived from studies of postmenopausal women, much less from studies of men, and less yet from studies of the CLD population.5,6 In particular, men with CLD comprise a high-risk group for fracture and have unique epidemiologic and clinical...
attributes. These attributes include the use of inhaled or oral glucocorticoids, decreased exercise, impaired gonadal hormone production, compromised pulmonary function, and others. Understanding the relative contribution of demographic and clinical variables to bone loss in patients with CLD would augment the prediction of fracture risk in these patients and would help in the selection of those who would benefit from bone densitometry screening.

We evaluated the contribution of clinical and demographic variables to bone loss in men with CLD by studying a population of outpatients cared for at the Atlanta VA Medical Center. These subjects had received chronic treatment with oral glucocorticoids, inhaled glucocorticoids, or no glucocorticoids. In addition, we simultaneously evaluated bone mass in a group of control subjects from the same medical center who did not have documented pulmonary disease. Our results revealed that CLD itself is a major risk factor for bone loss and that the magnitude of bone loss after chronic use of inhaled glucocorticoids is similar to the loss after chronic oral glucocorticoid therapy. We found that important correlates of bone loss included body mass index (BMI), serum estradiol-17β, and elevated N-telopeptide levels.

**Materials and Methods**

**Subjects**

From November 1996 to September 1998, 171 subjects between the ages of 23 and 90 years old were recruited from the outpatient population of the Atlanta VA Medical Center. After informed consent, the subjects were interviewed, their medical charts were reviewed, and other information was obtained from an electronic database of laboratory values and pharmacy records. The subjects contributed blood and urine specimens for biochemical and hormone assays and underwent dual-energy X-ray absorptiometry (DEXA) evaluation of the spine and left hip with the exception of total alkaline phosphatase, which was measured in the clinical pathology laboratories of Emory University; Lawrenceville, GA). The remaining laboratory assays were performed by Assay Services (Yerkes Primate Field Station; Emory University, Lawrenceville, GA). The remaining laboratory assays were performed in the clinical pathology laboratories of the Atlanta VA Medical Center.

**Variables Measured**

The historical and demographic variables analyzed included age, race, duration of respiratory illness, BMI, activity level (subjective-hours walked per day), smoking, consumption of coffee, concurrent illnesses, fracture history, and family history of osteoporosis. Information on the use of inhaled or oral glucocorticoids was derived from subject interviews, medical record reviews, and a 4-year electronic pharmacy record. Clinical variables included FEV1 and FVC, when available, for the CLD subjects. The severity of airflow obstruction was assessed according to American Thoracic Society criteria. Data was available for CBC count, electrolytes, serum aspartate aminotransferase, lactate dehydrogenase, total bilirubin, calcium, phosphate, random glucose, total testosterone, free testosterone, and estradiol-17β. The measured metabolic markers of bone turnover included total serum alkaline phosphatase, bone-specific alkaline phosphatase, and osteocalcin as osteoblast markers of bone formation, and urinary excretion of type I collagen crosslinks (N-telopeptide) as a marker of bone resorption.

**Assays**

Assays for gonadal steroids and metabolic markers of bone turnover, with the exception of total alkaline phosphatase, were performed by Assay Services (Yerkes Primate Field Station; Emory University, Lawrenceville, GA). The remaining laboratory assays were performed in the clinical pathology laboratories of the Atlanta VA Medical Center.

**Statistics**

For continuous variables, differences between groups were compared using analysis of variance (ANOVA); post hoc multiple comparisons were done using Scheffe's method. χ2 analysis was used to compare categorical variables. Relationships between bone density and other variables were determined using simple and multiple linear regression with stepwise variable selection. Pearson product-moment correlation coefficients are reported. Using predefined criteria for osteoporosis, logistic regression was used to calculate adjusted odds ratios for the presence of osteoporosis. All calculations were done using appropriate software (StatView Version 5.0; SAS Institute; Cary, NC).

**Results**

**Demographic and Clinical Characteristics**

The CLD subjects were not more likely to drop out of the study than the control subjects, suggesting that health status did not bias participation in the study (failure to report for DEXA after recruitment: CLD, 27%; control, 31.6% [p > 0.05 by χ2]). Table 1 shows selected demographic and clinical charac-
We did not find any difference in mean bone density within groups between subjects with asthma and those with COPD; therefore, bone mass data for COPD and asthma were pooled. Figure 1 shows BMD, Z scores, and T scores for the study subjects. All three CLD groups had reduced bone mass. A loss of bone mass in these subjects occurred whether or not they were prescribed chronic glucocorticoid therapy, as seen in the BMD data (Fig 1, top, A) and also in the T-score data (Fig 1, middle, B). Thus, CLD itself was associated with bone loss independent of glucocorticoid therapy. The subjects who were prescribed chronic inhalation glucocorticoid therapy had an overall loss of bone mass that was indistinguishable from those who were receiving oral therapy, a finding that was independent of age. The calculated odds ratios for meeting World Health Organization (WHO) criteria for the diagnosis of osteoporosis (T score < −2.5) after adjusting for BMI were calculated with their 95% confidence intervals (CIs) and are shown in Figure 2. The subjects with CLD were more than five times as likely to meet the criteria for osteoporosis as were the control subjects. The proportion of subjects with osteoporosis or osteopenia did not differ between groups treated with oral or inhaled glucocorticoids, suggesting that chronic use of inhaled glucocorticoids offered no protection from steroid-induced bone loss. The results were similar using the diagnostic criteria of the National Institutes of Health Consensus Development Conference (not shown). Overall, glucocorticoid-treated CLD subjects had a ninefold risk (95% CI, 0.78 to 30.7) of osteoporosis by WHO criteria, while those who were never treated with glucocorticoids had a fivefold risk (95% CI, 0.78 to 30.7).

**Relationship Between Bone Mass and Demographic or Clinical Variables**

We sought to identify demographic and clinical variables that were associated with low bone mass in our study subjects. Analysis of individual variables revealed that, for the study group as a whole, bone mass was positively correlated with BMI vs hip Z

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**Table 1—Historical and Demographic Data of Recruited Subjects by Group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I COPD/Oral</th>
<th>Group II COPD/Inhaled</th>
<th>Group III COPD/None</th>
<th>Group IV Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>52</td>
<td>34</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>Age, yr</td>
<td>62 ± 1.6</td>
<td>62 ± 1.7</td>
<td>64 ± 2.0</td>
<td>60 ± 1.8</td>
</tr>
<tr>
<td>Caucasian/African American, ratio</td>
<td>2.9</td>
<td>2.7</td>
<td>3.7</td>
<td>1.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.9 ± 0.9</td>
<td>26.9 ± 0.9</td>
<td>28.8 ± 1.0</td>
<td>30.3 ± 1.0</td>
</tr>
<tr>
<td>Exercise, subjective hours walked/d</td>
<td>2.2 ± 0.3†</td>
<td>3.4 ± 0.5</td>
<td>2.6 ± 0.3‡</td>
<td>5.0 ± 0.5</td>
</tr>
<tr>
<td>Smoking, pack-yrs</td>
<td>43.1 ± 6.4</td>
<td>33.6 ± 5.1</td>
<td>50.6 ± 11.0</td>
<td>29.5 ± 5.7</td>
</tr>
<tr>
<td>FEV₁, ‰</td>
<td>50.6 ± 2.8†</td>
<td>59.0 ± 3.7</td>
<td>68.9 ± 4.7</td>
<td>—</td>
</tr>
<tr>
<td>Caffeinated beverages, drinks/d</td>
<td>1.8 ± 0.4</td>
<td>2.0 ± 0.4</td>
<td>2.4 ± 0.4</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>Asthma patients, No.</td>
<td>7</td>
<td>13</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with alcohol consumption ≥ two drinks/d, No.</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Cumulative steroid dose (oral + inhaled), mg prednisone equivalent/4 yr</td>
<td>4,121 ± 617†</td>
<td>430 ± 70*</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM unless otherwise noted.
†p < 0.05 vs control subjects.
‡p < 0.05 vs group III.
score ($r = 0.346, p < 0.001$); BMI vs spine Z score
($r = 0.202, p < 0.01$); and weakly with exercise, activity, smoking, and
FEV$_1$. With the exception of BMI, no clinical or demographic variable was
independently correlated with bone mass by multiple regression in a model that included age, exercise,
smoking, caffeine use, duration of glucocorticoid use, % predicted FEV$_1$, and BMI. Thus, BMI ac-
counted for almost all of the predictive power for bone mass in these subjects. The relationship be-
tween BMI and bone mass is shown in Figure 3. The subjects with the lowest BMI tended to have
the lowest bone mass, as seen in the graph of BMI vs T score. The correlation between bone mass and BMI
was stronger for bone mass at the hip than at the spine, but it was significant at both sites for all three
measures of bone density. A small difference in mean BMI between groups was not significant
(mean ± SEM BMI: oral CLD, 28.9 ± 0.9; inhaled CLD, 26.9 ± 0.9; CLD, 28.9 ± 1.1; and control,
30.3 ± 1.0 [p > 0.05 by ANOVA]).

Relationship Between Bone Mass and Gonadal Hormones

Figure 4 shows serum testosterone, free testosterone, and estradiol-17β for the four study groups. When comparing all CLD subjects to control sub-

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**Figure 1.** Loss of bone mass in subjects with CLD. The graph shows the results of DEXA for study subjects expressed as follows: (top, A) areal BMD, (middle, B) T score (SD from peak bone mass), and (bottom, C) Z score (age-adjusted bone mass). I = CLD, oral glucocorticoids; II = CLD, inhaled glucocorticoids; III = CLD, no glucocorticoids; IV = control (no CLD or glucocorticoids); * = $p < 0.05$ vs group IV by Scheffe post hoc comparisons, ANOVA.
jects, the differences between groups for total and free testosterone were not statistically significant (mean ± SEM free testosterone, ng/mL: CLD, 10.0 ± 0.5; and control, 12.5 ± 0.8 [p > 0.05]). No differences were observed between individual groups in the mean total testosterone levels, although a trend for higher free testosterone level in the control group was observed (mean ± SEM total testosterone, ng/mL: oral, 318.6 ± 26.1; inhaled, 348.0 ± 28.6; none, 321.2 ± 42.7; and control, 405.1 ± 37.5; free testosterone, pg/mL: oral, 10.0 ± 0.7; inhaled, 9.8 ± 0.8; none, 10.1 ± 1.4; and control, 12.5 ± 0.8 [p > 0.05 by ANOVA]). The mean estradiol-17β level of the control group was significantly higher than that of the combined CLD groups (groups 1–3; estradiol-17β, pg/mL: CLD, 16.9 ± 1.4; and control, 27.3 ± 3.7 [p < 0.05]). This result was also confirmed by ANOVA, which showed the lowest estradiol-17β levels in the steroid-treated CLD subjects (mean ± SEM estradiol-17β, pg/mL: oral, 15.5 ± 2.5; inhaled, 16.6 ± 1.7; none, 20.5 ± 2.2; and control, 27.3 ± 3.7 [p < 0.05]). Figure 5 shows the relationship between estradiol-17β and bone mass at the hip. When all subjects were considered together, estradiol-17β was positively correlated with bone mass (r = 0.349, p < 0.001). Logistic regression revealed a significant inverse relationship between estradiol-17β and osteoporosis at both the hip and the spine using either NIH or WHO criteria.

Biochemical Markers of Bone Metabolism

A number of biochemical markers of bone metabolism were measured to determine their association with bone mass. We measured the bone formation markers osteocalcin and bone-specific or total alkaline phosphatase in serum, and the bone resorption marker N-telopeptide in a daytime spot urine sample. It was not always possible to time urine collection as the second morning void for N-telopeptide as recommended by the manufacturer of the assay (Ostex International; Portland, OR). However, the mean N-telopeptide level observed in our control group was similar to the normal values reported for

Figure 2. Odds ratios (OR) for achieving WHO criteria for the diagnosis of osteoporosis (T score < -2.5) in subjects with CLD. Results show the calculated OR ± 95% CI for each study group. The ordinate is drawn to depict the control group at an OR = 1.0.

Figure 3. The relationship between bone mass and BMI for subjects with CLD. The solid line shows the calculated relationship between hip Z score and BMI for all participants in the study with the exception of patients with OSA. The vertical dotted line indicates the normal median BMI for healthy men of the same average age as the study subjects (r = 0.362, p < 0.0001).

1620

Clinical Investigations
Bone mass was negatively correlated with N-telopeptide levels ($r = -0.252$, $p < 0.01$). The relationship between N-telopeptide and bone mass is shown in Figure 6. N-telopeptide was weakly correlated with bone-specific alkaline phosphatase levels but not with other biochemical markers, clinical or demographic variables, or gonadal steroid levels. No other biochemical markers of bone metabolism showed significant associations with the study variables. An N-telopeptide measurement of two SD above the mean (≥ 63 BCE/mM Cr) yielded an odds ratio of 4.0 (95% CI, 0.86 to 18.5) for a hip T score < 2.5. The positive predictive value of N-telopeptide was 36%, and the negative predictive value was 78%. As expected, additional routine clinical chemistry values (hematocrit, electrolytes, and liver enzymes) were not significantly correlated with bone mass.

**Discussion**

Osteoporosis continues to be a major problem in men with chronic illness, but the prevalence of low bone mass, the criteria for obtaining bone densitometry, and the impact on the health-care system remains unknown. This may be because most studies on osteoporosis focus on postmenopausal women rather than men. Indeed, current Medicare guidelines for reimbursement of bone densitometry are restricted to postmenopausal women and patients receiving glucocorticoids. In men with CLD, osteoporosis may be particularly disabling because vertebral fractures reduce vital capacity, which further compromises ventilation. An increased prevalence of vertebral fractures has been documented in men with CLD based on the evaluation of lateral spine films. Thus, we studied the prevalence of osteoporosis and variables that would contribute to the identification of CLD patients at risk for bone loss.

Bone mass measurements are currently used to identify patients at risk for fracture. The inverse relationship between bone mass and fracture risk, as measured by DEXA, has been established for postmenopausal women and is supported by more limited data in men. Using the WHO criteria of $T < -1.0$ for osteopenia and $T < -2.5$ for osteoporosis, our DEXA data show that the prevalence of osteopenia and osteoporosis in men with CLD is 72% and 36%, respectively. A comparison of DEXA measurements in CLD subjects with control subjects suggested a fivefold to ninefold increase in the prevalence of extensive bone loss (T score < 2.5) in CLD compared to subjects without CLD. Although we excluded subjects with known causes of bone loss from our control group, these subjects had other chronic illnesses, including cardiovascular disease, hypertension, dyslipidemia, and glucose intolerance. Thus, CLD itself increases the risk of osteoporosis.

A review of records revealed that some subjects with CLD had diagnoses of emphysema, chronic bronchitis, or asthma in addition to COPD. An analysis of bone density for the individual diagnoses did not reveal a difference in results or conclusions, with the exception of the subjects with OSA. These eight men had bone densities that were similar to subjects in the control group and were excluded from the analysis of CLD.

We determined the relative contribution of glucocorticoid treatment to the loss of bone mass by comparing DEXA measurements of CLD subjects who were prescribed oral (ie, oral and inhaled),
inhaled, or no glucocorticoids. Our data revealed that glucocorticoid therapy was associated with a ninefold increase in the proportion of subjects who fulfilled the WHO criteria for osteoporosis compared to CLD subjects that never took glucocorticoids, and a fivefold increase due to CLD itself. It is not known if glucocorticoids render bone more susceptible to fracture at any given bone density, an issue that could be resolved by measuring BMD and fracture prevalence in the same population. The loss of bone mass secondary to glucocorticoid therapy has been well documented previously. Most studies of

![Figure 5](image1.png)

**Figure 5.** The relationship between bone mass and serum estradiol-17β concentration. The solid line shows the calculated relationship between hip Z score and serum estradiol-17β concentration for all participants in the study ($r = 0.349, p < 0.001$).

![Figure 6](image2.png)

**Figure 6.** The relationship between bone mass and urine N-telopeptide level. The solid line shows the best fit between the Z score and urine N-telopeptide for all participants in the study ($r = 0.224, p < 0.005$).
glucocorticoid-induced osteoporosis report an accelerated loss of bone during the first year of therapy. LoCascio et al reported a 30% loss of bone mass during the first 12 months of glucocorticoid therapy, followed by a 1 to 7% loss per year thereafter. Our subjects who were prescribed chronic oral or inhaled glucocorticoids had the lowest age-adjusted bone mass; nevertheless, reduced BMD was a feature of CLD regardless of glucocorticoid use. Overall, the subjects who were prescribed oral glucocorticoids had a tenfold-greater cumulative dose during the prior 4 years than those using inhaled therapy. The similarity in BMD and prevalence of osteoporosis in the oral and inhaled groups suggests that the deleterious effect of chronic glucocorticoid therapy on the skeleton is already maximal with the lower inhalation therapy dose.

We also found that subjects with CLD who had not been treated with glucocorticoids had a relatively greater reduction in bone mass at the hip than at the spine. Studies that report changes in bone mass following the initiation of glucocorticoid therapy have shown a relatively greater reduction in bone mass at the spine because of the more rapid turnover of vertebral cancellous bone. Our subjects used glucocorticoids for an average of 1.5 years and 2 years (groups 1 and 2, respectively). Thus, the distribution of bone loss we observed is not explained by a more prolonged exposure to glucocorticoids than the previously described acute loss. Patients with CLD may be at a greater risk for bone loss at the hip, in part because of decreased ambulation and loading at this site. All of our CLD patients had subjectively decreased exercise compared to the control subjects, as measured by the number of hours walked per day.

Other studies have suggested a prominent effect of CLD on the vertebral fracture rate independent of steroid use. McEvoy et al reported that the proportion of CLD patients with vertebral fractures was 49%, 57%, and 62% for those receiving no glucocorticoids, for those receiving inhaled glucocorticoids, or for those receiving oral glucocorticoids, respectively. Although the study by McEvoy et al did not include a control group for comparison, the prevalence of vertebral fractures in men > 50 years old has been reported to be from 15 to 20%. These fracture results and our data on DEXA screening suggest that patients with CLD would benefit from bone density screening regardless of glucocorticoid use.

A large number of clinical and biochemical variables were measured to determine if they were correlated with bone mass. Of these, only BMI was positively correlated with bone mass independent of other variables. It is noteworthy that subjects with the lowest bone mass had a BMI clustering below the normal median value. This may indicate that the loss of bone mass from chronic CLD occurs once the disease is severe enough to cause weight loss. A recent analysis of the National Health and Nutrition Examination Survey I prospective data revealed that the relative risk of hip fracture in men was significantly related to three variables: a 10% loss of body weight during follow-up, the presence of one or more chronic medical conditions, and low bone density at onset. Our results support the conclusion that patients with a low BMI are at a particularly high risk for osteoporotic fracture, and a BMI below median for age may add to the suspicion of increased fracture risk.

For both women and men, gonadal hormone status is an important determinant of skeletal health. The osteoporotic effect of hypogonadism and its reversal by androgen treatment in men has been accepted for some time. Several recent reports have suggested that estrogen, rather than testosterone, may be the gonadal hormone active in bone that maintains a positive formation/resorption balance. This hypothesis is supported by the report that estrogen, rather than free or total testosterone, is most correlated with bone mass in elderly men. Furthermore, aromatase deficiency has been associated with severe osteoporosis that responds to estrogen treatment. We measured total and free testosterone and estradiol-17β to determine if hypogonadism contributed to loss of bone mass in our subjects and to determine the proportion that developed hypogonadism among users of oral glucocorticoids. CLD subjects, as a group, had significantly lower estradiol levels than control subjects. We did not observe a difference in total testosterone between our control and CLD groups. The correlation between estradiol-17β and bone mass for all study subjects provides further support for the estrogen hypothesis, since this correlation was not evident for total or free testosterone. The relationship between estradiol-17β and bone mass was strongest for those receiving oral glucocorticoids and was significantly related to the total accumulated glucocorticoid dose, which is in agreement with the known effect of glucocorticoids as inhibitors of gonadal steroid production.

Recently, biochemical measures of bone metabolism have become available as adjunct tests for the evaluation of skeletal health in women, although these have not been evaluated as predictors of low bone mass in men with CLD. Of the markers we measured, only N-telopeptide was significantly correlated with bone mass. N-telopeptide was a weak predictor of low bone mass in our study. Others have reported that N-telopeptide accurately shows the early response to therapy in men receiving testoster-
one replacement; however, random levels have not yet been shown to be diagnostic of osteoporosis.33

In conclusion, patients with CLD comprise a high-risk group for osteoporosis. In comparison to postmenopausal women, for whom the prevalence of osteoporosis has been estimated to be 30%,34,35 men with CLD have an almost identical burden of disease. Recent prospective data12 suggest that the relationship between BMD and fracture incidence is the same for men and women. Thus, it would be prudent to consider men with CLD for bone densitometry screening even if they are not treated with glucocorticoids. Further studies will be needed to determine additional risk factors associated with bone loss and the exact relationship between BMD and fracture rate in CLD.

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REFERENCES

5 Ross PD. Osteoporosis: frequency, consequences, and risk factors. Arch Intern Med 1996; 156:1399–1411