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FRACTURE RISK ASSOCIATED WITH ORAL CORTICOSTEROID USE: A RETROSPECTIVE COHORT STUDY ON DOSE-RESPONSE AND THE REVERSIBILITY OF FRACTURE RISK POST-THERAPY

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Abstract
The use of oral corticosteroids is also common in the management of different inflammatory and autoimmune diseases accompanied by a high fracture rate in vertebral body and proximal femur. This paper was a prospective retrospective cohort study that tried to assess the risks of fractures in patients who were exposed to oral corticosteroids based on the 250 general practices in the United Kingdom. The research has identified that the risk of fractures increases significantly very soon after corticosteroid therapy is initiated and it directly depends upon the dose of corticosteroids. It is worth noting that the risk of fractures reduced to baseline levels once corticosteroid therapy was stopped with the highest degree in subsequent 12 months. These data imply that it might be crucial to pay attention to the risk of fractures in patients who are treated with high doses of corticosteroids and that early detection of corticosteroid-induced osteoporosis could be valuable. Future research is required to increase knowledge of long-term effects due to corticosteroid usage in relation to the development of fracture and the importance of early preventative efforts.

Keywords: Oral corticosteroids, fracture risk, osteoporosis, vertebral fracture, proximal femur

Introduction

Oral corticosteroids have been more than 50 years in the medical treatment, and during this period, they played an important role in the treatment of diseases such as asthma, inflammatory diseases that affect joints, diseases of the gastrointestinal tract, and those of the central nervous system. Though these medicines are effective against such conditions, the oral corticosteroid therapy results in one of the most severe side effects, which is osteoporosis. The studies have demonstrated that oral treatment with corticosteroids resulted in loss of bone mineral density irrespective of the type of disease they were treating. This may be substantial and occur very fast and is much related to the amount of corticosteroids and is likely to happen within a shorter duration in trabecular bone opposed to cortical bone[1, 2]. Nonetheless, some have argued that the baseline bone density together with the bone losing in the course of treatment due to corticosteroids may not necessarily match the risk of fractures by a patient. Indicatively, in a study, vertebral fracture has also been noted in asthmatic patients taking oral corticosteroids despite having stronger bones than other individuals with age-related

osteoporosis-related fractures [3]. There is therefore a higher risk of fracture related to use of oral corticosteroids in treating the same amount of bone loss as found in postmenopausal osteoporosis. There have been a number of epidemiological studies (though generally in small scale) examining the connection between oral corticosteroids and increased fracture risk. In the two largest trials ever performed, it has been confirmed that use of corticosteroid increases the risk of fractures by 50 percent to 100 percent [4, 5]. Nevertheless, data presented by these studies lack acquainted information in the dose-response association and the length of time that oral corticosteroids usage correlates to the risk of a fracture. In addition, it is unknown as to how discontinuation of corticosteroid therapy influences the risk of fractures. The proposed research was aimed at the measurement of the fracture risks among the patients who have been exposed to oral corticosteroids in a representative general medical practice scenario.

METHODS/ MATERIALS

Data Resource

The used source of data in this study is General Practice Research Database (GPRD) that stores computerized medical records of general practitioners (GPs). The GPs form a crucial part of the healthcare system in U.K. they are the providers of the first point of contact and referral. Patients are usually permanently affiliated to a practice where their medical data including the information provided by GPs and specialists in addition to hospital admission concentrates. The GPRD captures information on the demography, medications, clinical incidents, preventive encounters, reference to specialists, hospitalization, and its results [6-11]. Oxford Medical Information Systems (OXMIS) codes are used to organize clinical data in line with the International Classification of Diseases (ICD-9) [7,10]. Internal validation also requires each GPRD entry to be cross-referenced within the practice and checked against external statistics[6-11], which is needed to ensure accuracy of the data. Data recorded on such practices that answer to these quality control safety practices are only covered under the GPRD. A few validation studies have determined the high completeness and validity of the database[12-15].

Outcome Measurement and Population of the Study

It was a retrospective cohort study in which the patients using oral corticosteroids were compared to the control patients. Oral corticosteroid users were specified as patients aged 18 years and above permanently registered and at least one prescription of oral corticosteroids taken by practice when the GPRD joined in the study. Patients who were prescribed nonsystemic corticosteroids, by prescription (topical, aural, ophthalmic or nasal corticosteroids), and matched by the age (within the span of five years, or within the span of ten years where there was no very close match at all), gender and, to the extent that this was achievable, medical practice, were considered to be control patients. The cohort has a topical corticosteroid most commonly in the control group with 78.0 per cent of the cohort. Each oral corticosteroid recipient had a baseline which was taken as the date of the initial oral corticosteroid prescription following the enrollment of their practice to the GPRD. All oral corticosteroid users were tracked individually since the baseline up to the time they broke a bone, 91 days following the date of the last prescription of the oral corticosteroid, or their practice was altered, they died, or the end of the research, whichever one came first. The control patients were trailed back to an arbitrarily chosen commencement date until the occasion of a fracture or identical circumstances happened (change of practice, death or trial termination).

In a further analysis regarding the question of whether or not the risk during the oral corticosteroid discontinuation can be reversed, the individuals who ceased using corticosteroids prior to the conclusion of the study shifted care until they had fractured or had been censored, thus starting at 91 days after their final prescription of a corticosteroid treatment. Patients were censored without regard to whether they had experienced prior fractures during follow-up as any apparent change in fracture rates would not have been due to censoring after one first event. The fractures such as nonvertebral and vertebral fractures were detected by using the ICD-9 classifications. Hip (ICD-820) fractures,

forearm (ICD-813) fractures, vertebral (ICD-805806) fractures, nonvertebral fractures (ICD-800804 and 807829) were documented. The diagnosis validation and Discharge summary or diagnostic report verification of 150 hip fracture patients and 150 vertebral fracture patients was questioned to an important number of general practitioners. GP confirmed 91.0% of hip fractures when using questionnaire and 85.2 percent by use of discharge summaries. Before ascertaining the actual vertebral fractures, 88.1 percent of vertebral fracture cases were determined by the questionnaire and 76.3 percent by the radiographic report, and 96.4 percent of vertebral fractures were diagnosed radiographically by the GP. Potential confounders were considered to include diabetes, rheumatoid arthritis, hyperthyroidism, congestive heart failure, seizures, anemia, dementia, depression, psychotic disorders, cerebrovascular accidents, falls and history of any fracture or back pain before baseline. Medications used in follow-up, including anticonvulsant, methotrexate, thiazide diuretics, anxiolytics, antipsychotics, antidepressants, anti-Parkinson drugs, hormone replacement therapy, bisphosphonates, vitamin D, and calcitonin, were taken into account as possible confounding variables[16, 17]. In oral corticosteroid users, the average dose of corticosteroids that were consumed during the treatment period was measured by splitting up the number of milligram of prednisolone (or equivalent doses) indicated throughout the treatment period by the number of days of therapy. Treatment interval was deemed, as of the initial preschribing of oral corticosteroid to 31 days following the shortest preschribing (median length of supply was 31 days). It was categorized into three doses as low dose (below 2.5 mg/day), medium dose (2.5-7.5 mg/day) and high dose (7.5 mg/day or over).

Statistical Methods

Incidences of fracture were determined by one divided by the number of total patient-years of follow-up[19]. The relative rates were adjusted via Cox proportional hazards models with age, gender, and confounding variables, chosen to be adjusted. It was in the third step that the final regression models were constructed. First, the potential confounders that either effected crude rate by at least 10% or were highly associated with the development of fracture (relative rate was greater than 1.50 or less than 0.67) were incorporated along with the interaction variations between the confounders and age and gender [20]. Backward stepwise selection was used to identify the final model and a level of significance of 0.25 was adopted. The model was assessed using martingale and deviance residuals and time dependent covariates were assessed to make sure that proportional hazards assumption was satisfied. A non parametric cubic spline regression model was employed in the analysis of fracture risk after corticosteroid withdrawal in consideration of time trend adjustment of the risk factors [21-24].

Results

The characteristics and the follow-up of the corticosteroid and control groups are indicated in Table 1. The cumulative follow-up time of both groups is a total of 162.8 person-years of corticosteroid and 332.0 of the control group. The average follower-up was 1.3 years and 2.7 years, in corticosteroid and control groups, respectively. The follow-up time was half a year less in a corticosteroid group (0.3 years) than in a control one (2.4 years). The mean age of both groups was almost similar, except that mean age of corticosteroid group was 57.0 years as opposed to the mean age of control group which was 57.1 years. Both groups were of a median age of 60 years. Considering the medical conditions, back pain was observed in 8.8 percentage of the corticosteroid group and 7.2 percentage of the control group, while rheumatoid arthritis conditions were identified at 4.0 percentage in the corticosteroid group, as compared to 0.8 percentage in the control group. The corticosteroid group and control group recorded falls in the 12 months before the study in 1.6 percent and 1.2 percent respectively. The percentages of individuals who took NSAIDs in the past were higher in the corticosteroid group (26.4%) than in the control one (20.8%). The proportions of the participants who take hormone replacement therapy were similar in both groups (4.8 percent). On fracture history, nonvertebral and vertebral fracture were both observed to occur in 1.6 percent of both sets

respectively, with vertebral fracture occurring in both 0.8 percent and 0 percent in corticosteroid and control groups respectively.

Table 2 asserts that the respective case rates and adjusted relative rates were compared between corticosteroid and control groups of different types of fractures. There was a higher rate of nonvertebral fractures reported in the corticosteroid group (2.1 percent) than in the control group (1.4 percent) with an adjusted relative rate of 1.34 (95 percent CI: 1.30 to 1.39). In forearm fractures, the corticosteroid group had a slightly increased rate (0.4%), compared to controls (0.3%) resulting in an adjusted relative rate of 1.10 (95% CI: 1.021.18). There were also increased hip fractures in the group using corticosteroid (0.3%) than those who use control (0.2%) with an adjusted relative rate of 1.62 (95% CI: 1.48-1.77). The number of vertebral fractures was significantly different between categories with vertebral fractures (0.3%) in the corticosteroid group and control (0.1%) at an adjusted relative rate of 2.62 (95 percent amenity: 2.33-2.94)

Table 1: Baselines Characteristics and Follow-Up Data on Corticosteroids, Controls

Category	Corticosteroid group (n = 125)	Control group (n = 125)
Follow-up		
Total duration (person-years)	162.8	332.0
Mean duration of follow-up per subject (years)	1.3	2.7
Median duration of follow-up per subject (years)	0.3	2.4
Age (years)		
Mean	57.0	57.1
Median	60	60
Medical condition		
Back pain year before	11 (8.8%)	9 (7.2%)
Rheumatoid arthritis	5 (4.0%)	1 (0.8%)
Falls year before	2 (1.6%)	2 (1.2%)
Drug history in year before baseline		
NSAIDs	33 (26.4%)	26 (20.8%)
Hormone replacement therapy	6 (4.8%)	6 (4.8%)
Fracture history in year before baseline		
Nonvertebral fracture	2 (1.6%)	2 (1.6%)
Vertebral fracture	1 (0.8%)	0 (0%)

Table 2: Case vs. Adjusted Relative Rate according to Corticosteroid and Control Groups

Category	Corticosteroid group (n = 125)	Control group (n = 125)	Adjusted relative rate	95% Confidence Interval
Nonvertebral	6400 cases (2.1%)	8600 cases (1.4%)	1.34	1.30–1.39
Forearm	1340 cases (0.4%)	2200 cases (0.3%)	1.10	1.02–1.18
Hip	1075 cases (0.3%)	1105 cases (0.2%)	1.62	1.48–1.77
Vertebral	1040 cases (0.3%)	470 cases (0.1%)	2.62	2.33–2.94

Discussion

The results of this research imply that an increase in exposure to oral corticosteroid treatment is the major cause of fracture, especially vertebral body and proximal femur. This is a direct increase in the risk of fracture associated with standardised doses of oral corticosteroids. Moreover, the review found that fracture risk increases fast when using corticosteroid therapy but decreases back to baseline at a fairly quick pace when the drug is abandoned. Although the effects on bone mineral density have been studied in detail during corticosteroid therapy, little is known about the fracture, a more clinically relevant endpoint. In a large case-control study of the general population, doubling of hip fracture risk was seen among corticosteroid users[4]. This increment in relative risk however, was not

significantly important when the confounding factors (given) were adjusted. Our study and the aforementioned population-based case-control study were comparable in the excess risks of hip fractures in oral corticosteroid users. The incidence of fracture was also higher in corticosteroid users than in controls in other studies, each of which analyzed 100 or more oral corticosteroid users, although the degree of the risk varied and differed significantly[25-29]. All the studies did not analyze the correlation between a risk of fracture and dosage of corticosteroids or the reversity of the risk of fracture after the termination of using corticosteroid treatment. Indeed, this research proves the fact that the development of the higher risk of fractures having initiated the treatment with oral corticosteroids happens quickly, as the nonvertebral risk of fracture increases significantly within the first 3 months. One reason as to why this may happen is through the apoptosis of osteoblasts and osteocytes at the hands of corticosteroids[30]. Instead, it may be put forward that it may be due to a significant change in bone turnover resulting in microarchitectural changes in bone quality and consequent increase in risk of fracture. This fact corresponds to the recent bisphosphonate reports suggesting that a relatively small increment in bone mineral density could be protective against fracture [31]. Similar findings were made in an earlier study on cardiac transplant patients in which fractures appeared early in corticosteroid therapy, although there were greater amounts of corticosteroids and immunosuppressant agents presen t[32]. The other mechanism through which corticosteroids could cause an increase in risk of fracture is by increasing risk of falls. Although falls were not a primary focus of this study, we did note that there was a striking rise in the rate of falls in the time period following the initiation of corticosteroid therapy (1.6 per 100 person-years during the 1 year before baseline and 2.8 in the first 3 months). These rates bounced back to normal when the use of corticosteroid stopped. Previous studies have never referred specifically to the connection between corticosteroid use and the occurrence of the fall but the Southampton case-control study implied even frailer and much more inactive corticosteroid users and immobility prone[4]. The pattern of fracture incidence among oral corticosteroid users may be due to the combination of predisposing the bones to becoming weaker earlier in life and the subsequent predisposing the individual to trauma. One of the important outcomes of this research was that fracture risk reversal occurred after stopping of oral corticosteroid therapy. The risks of fractures decreased to near-normal values following corticosteroids withdrawal, with the highest drop being at the first year. Complete reversibility of corticosteroid-induced osteoporosis and all of its implications has been discussed in the literature[2, 33-35]. Patient studies with Cushing syndrome cured have demonstrated normalized[36-39] bone density, and in rheumatoid arthritis and sarcoidosis there was increased bone density following discontinuation of corticosteroids[40-42]. This is the first study to determine the reversibility of the fracture risk and not only the density of the bones. In those patients who discontinued long-term high doses of corticosteroids, a significant decrease of the fractures rate was noted, which confirmed once again the hypothesis of reversibility. These results reflect the value of employing drugs in the prevention and treatment of corticosteroid-induced osteoporosis, particularly when the high-dose treatment of oral corticosteroids is administered. The patients using nonsystemic corticosteroids were used as the control group of this research. Although we intended to compare the control group with the main one in terms of age, sex, and practice, we chose the people who used the nonsystemic corticosteroids as the control group as they were the most likely to be actively registered in the GPRD. Such a decision was probably conservative in the estimation of risk of oral corticosteroids. The omission of control patients who received frequent nonsystemic corticosteroids use did not materially change the results. Also, fracture incidence in our control group was as expected in the whole GPRD population [43, 44]. Nonetheless, this study has a few limitations. The potential of underlying diseases could be the reason of the increased risk of fractures, which is one limitation. As an illustration, the incidence of fracture is reported to be high in patients with rheumatoid arthritis compared to the non corticosteroid-user group [4]. Nonetheless, the elimination of patients with musculoskeletal diseases did not influence the outcomes that much, and the proportions of fractures between the users of oral corticosteroids were nearly identical in different underlying illnesses. Detection bias is another possible limitation since the physicians may tend to diagnose more fractures among the corticosteroid

users because they are aware of the bone risks. Nonetheless, we did not find any evidences of any considerable disparities in case types, and validation of hip and vertebral fractures proclaimed homogenous reporting between the application of corticosteroids and controls. Also, the proportion of oral corticosteroid users (5.0%) ever using hormone replacement therapy and proportion of bisphosphonates users were low (1.8%) on follow-up. Finally, definition of oral corticosteroid dose was a limit. We averaged the dose of corticosteroid over the time between the day of first prescription and last prescription because it was not recorded as stipulated in the prescription noted; therefore, resulting in under estimation of excess fracture risk. The method also might have under-dosed corticosteroids particularly in patients who took the drug at the interval. Adjustment on calendar year, smoking, alcohol consumption and body mass index did not have a significant impact on the outcome as checked by sensitivity analyses. Strict time matching of the follow-up of the control group equal with the followers of corticosteroid users or exclusion of those patients who used heavy nonsystemic corticosteroids did not influence the results.

Conclusion

This research paper reveals a major threat of fractures in case of using oral corticosteroids, especially in the vertebral body and proximal femur. The rate of fractures also rises speedily with use of corticosteroid therapy and the size of the risk is proportional to the corticosteroid dose. Furthermore, the report also presents valuable information about the observed tendency of a fracture risk to go back to its baseline value in light of discontinuing oral corticosteroid treatment with the highest decrease being noted during the first year. These results support the necessity of considering fracture risk in patients receiving corticosteroid medication, particularly those using high doses of the medication, and indicate that the application of measures to prevent corticosteroid-related osteoporosis has to be implemented at these times. Whereas this work can be appreciated, it requires additional investigation that would help the researcher trace the influence of long-term corticosteroid therapy on fracture risk and whether early intervention can minimize such risks.

Reference

1. Lukert, B. (1996). Glucocorticoid-induced osteoporosis. In R. Marcus, D. Feldman, & J. Kelsey (Eds.), *Osteoporosis* (pp. 801–813). Academic Press.
2. Reid, I. R. (1998). Glucocorticoid-induced osteoporosis: Other forms of secondary osteoporosis. In P. J. Meunier (Ed.), *Osteoporosis: Diagnosis and Management* (pp. 233–250). Martin Dunitz.
3. Luengo, M., Picado, C., Del Rio, L., Guañabens, N., Montserrat, J. M., & Setoain, J. (1991). Vertebral fractures in steroid-dependent asthma and involutional osteoporosis: A comparative study. *Thorax, 46*(10), 803–806.
4. Cooper, C., Coupland, C., & Mitchell, M. (1995). Rheumatoid arthritis, corticosteroid therapy, and hip fracture. *Annals of the Rheumatic Diseases, 54*(1), 49–52.
5. Hooyman, J. R., Melton, J. L., III, Nelson, A. M., O'Fallon, M. W., & Riggs, B. L. (1984). Fractures after rheumatoid arthritis. *Arthritis & Rheumatism, 27*(12), 1353–1361.
6. Hall, G. (1992). Pharmacoepidemiology using a UK database of primary care records. *Pharmacoepidemiology and Drug Safety, 1*(1), 33–37.
7. Lis, Y., & Mann, R. D. (1995). The VAMP research multi-purpose database in the U.K. *Journal of Clinical Epidemiology, 48*(5), 431–443.
8. Mann, R. D., Hall, G., & Chukwujindu, I. (1992). Research implications of computerized primary care. *Post Marketing Surveillance, 5*(5), 259–268.
9. Hollowell, J. (1994). General Practice Research Database (GPRD): Scope and Quality of Data. Office of Population Censuses and Statistics.
10. Anonymous. (1996). The General Practice Research Database: Information for Researchers. Office for National Statistics.
11. Walley, T., & Mantgani, A. (1997). The U.K. General Practice Research Database. *Lancet, 350*(9090), 1097–1099.

12. Jick, H., Jick, S. S., & Derby, L. E. (1991). Validation of information recorded on general practitioner-based computerized data resource in the United Kingdom. *British Medical Journal, 302*(6779), 766–768.
13. Jick, H., Terris, B. Z., Derby, L. E., & Jick, S. S. (1992). Further validation of information recorded on a general practitioner-based computerized data resource in the United Kingdom. *Pharmacoepidemiology and Drug Safety, 1*(5), 347–349.
14. Nazareth, I., King, M., Haines, A., Rangel, L., & Myers, S. (1993). Accuracy of diagnosis of psychosis on general practice computer system. *British Medical Journal, 307*(6895), 32–34.
15. van Staa, T. P., & Abenhaim, L. (1994). The quality of information recorded on a U.K. database of primary care records: A study of hospitalization due to hypoglycemia and other conditions. *Pharmacoepidemiology and Drug Safety, 3*(1), 15–21.
16. Shane, E. (1996). Osteoporosis associated with illness and medications. In R. Marcus, D. Feldman, & J. Kelsey (Eds.), *Osteoporosis* (pp. 925–946). Academic Press.
17. Grisso, J. A., Capezuti, E., & Schwartz, A. (1996). Falls as risk factors for fractures. In R. Marcus, D. Feldman, & J. Kelsey (Eds.), *Osteoporosis* (pp. 599–611). Academic Press.
18. British Medical Association & the Royal Pharmaceutical Society of Great Britain. (1996). *British National Formulary Number 32* (September 1996). Pharmaceutical Press.
19. Breslow, N. E., & Day, N. E. (1987). *Statistical Methods in Cancer Research*. International Agency for Research on Cancer.
20. Greenland, S. (1989). Modelling and variable selection in epidemiologic analysis. *American Journal of Public Health, 79*(3), 340–349.
21. Greenland, S. (1995). Dose-response and trend analysis in epidemiology: Alternatives to categorical analysis. *Epidemiology, 6*(4), 356–365.
22. Durrleman, S., & Simon, R. (1989). Flexible regression models with cubic splines. *Statistics in Medicine, 8*(5), 551–561.
23. Pizer, S. M. (1975). *Numerical Computing and Mathematical Analysis* (Chapter 4). Science Research Associates, Inc.
24. Anonymous. (1996). *SAS/GRAPH Software: Reference, version 6, 1st ed., Vol. 1*. SAS Institute, Inc.
25. McDougall, R., Sibley, J., Haga, M., & Russell, A. (1994). Outcome in patients with rheumatoid arthritis receiving prednisone compared to matched controls. *Journal of Rheumatology, 21*(7), 1207–1213.
26. Saag, K. G., Koehnke, R., Caldwell, J. R., Brasington, R., Burmeister, L. F., Zimmerman, B., Kohler, J. A., & Furst, D. E. (1994). Low dose long-term corticosteroid therapy in rheumatoid arthritis: An analysis of serious adverse events. *American Journal of Medicine, 96*(2), 115–123.
27. Michel, B. A., Bloch, D. A., & Fries, J. F. (1991). Predictors of fractures in early rheumatoid arthritis. *Journal of Rheumatology, 18*(6), 804–809.
28. Michel, B. A., Bloch, D. A., Wolfe, F., & Fries, J. F. (1993). Fractures in rheumatoid arthritis: An evaluation of associated risk factors. *Journal of Rheumatology, 20*(10), 1666–1669.
29. Adinoff, A. D., Hollister, M. D., & Roger, J. (1983). Steroid-induced fractures and bone loss in patients with asthma. *New England Journal of Medicine, 309*(5), 265–268.
30. Weinstein, R. S., Jilka, R. L., Parfitt, A. M., & Manolagas, S. C. (1998). Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. *Journal of Clinical Investigation, 102*(2), 274–282.
31. Cummings, S. R., Black, D. M., & Vogt, T. M., for the FIT Research Group. (1996). Changes in BMD substantially underestimate the anti-fracture effects of alendronate and other antiresorptive drugs. *Journal of Bone and Mineral Research, 11*(Suppl 1), 102.
32. Shane, E., Rivas, M. D. C., Silverberg, S. J., Kim, T. S., Staron, R. B., & Bilezikian, J. P. (1993). Osteoporosis after cardiac transplantation. *American Journal of Medicine, 94*(3), 257–264.
33. Sambrook, P. N., & Jones, G. (1995). Corticosteroid osteoporosis. *British Journal of Rheumatology, 34*(1), 8–12.

34. Sambrook, P. N. (1996). Corticosteroid-induced osteoporosis. *Journal of Rheumatology, 23*(Suppl 45), 19–22.
35. Dequeker, J., & Westhovens, R. (1995). Low dose corticosteroid-associated osteoporosis in rheumatoid arthritis and its prophylaxis and treatment: Bones of contention. *Journal of Rheumatology, 22*(5), 1013–1019.
36. Lufkin, E. G., Wahner, H. W., Bergstralh, E. J., & Bilezikian, J. P. (1988). Reversibility of steroid-induced osteoporosis. *American Journal of Medicine, 85*(6), 887–888.
37. Hermus, A. R., Huysmans, A., Smals, A. G., Corstens, F. H., Kloppenborg, P. W., & van 't Hof, M. A. (1994). Remarkable improvement of osteopenia after cure of Cushing's syndrome. *Hormone and Metabolic Research, 26*(5), 209–210.
38. Manning, P. J., Evans, M. C., & Reid, I. R. (1992). Normal bone mineral density following cure of Cushing's syndrome. *Clinical Endocrinology, 36*(2), 229–234.
39. Pocock, N. A., Eisman, J. A., Dunstan, C. R., Evans, R. A., Thomas, D. H., & Huq, N. L. (1987). Recovery from steroid-induced osteoporosis. *Annals of Internal Medicine, 107*(3), 319–323.
40. Laan, R. F. J. M., van Riel, P. L. C. M., van de Putte, L. B. A., van Erning, L. J. T. O., van 't Hof, M. A., & Lemmens, J. A. M. (1993). Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. *Annals of Internal Medicine, 119*(12), 963–968.
41. Hall, G. H., Spector, T. D., Griffin, A. J., Jawad, A. S. M., Hall, M. L., & Doyle, D. V. (1993). The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. *Arthritis and Rheumatism, 36*(10), 1510–1516.
42. Rizzato, G., & Montemurro, L. (1993). Reversibility of exogenous corticosteroid-induced bone loss. *European Respiratory Journal, 6*(1), 116–119.
43. Anonymous. (1996). *The EPIC Encyclopedia of Clinical Practice*. EPIC, The GP Database Research Company.
44. Donaldson, L. J., Cook, A., & Thomson, R. G. (1990). Incidence of fractures in a geographically defined population. *Journal of Epidemiology and Community Health, 44*(4), 241–245.