ORIGINAL ARTICLE

The effect of bisphosphonate on prevention of glucocorticoid-induced osteoporosis

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Abstract

Background: Glucocorticoid therapy can induce osteoporosis. Bone mineral density (BMD) measurement has been used to assess the risk of fracture in these patients. The most important mechanism is diminished bone formation mainly at the sites with trabecular bone. The objective of this study is to evaluate the effect of alendronate on prevention of glucocorticoid-induced osteoporosis.

Methods*:* During 18 months, in a prospective clinical trial, 72 patients with autoimmune disease were randomly divided into 2 equal groups. Group 1 (n=36) was treated with oral vitamin-D, 50000 IU twice weekly and calcium, 500 mg twice daily. Group 2 (n=36) was treated with oral vitamin-D, 50000 IU twice weekly, calcium, 500 mg twice daily, and alendronate, 10 mg per day. The patients were followed clinically, undergoing densitometry and X-ray of the spine and hip area for 18 months.

Results: Change of BMD in the lumbar spine after 18 months of therapy was -1/67% and +2.4% in groups 1 and 2, respectively. Change in femoral neck BMD was -2.1% in group 1 and +1.8% in group 2.

Conclusion: The administration of alendronate plus vitamin D and calcium was more effective in preventing bone loss due to glucocorticoid-induced osteoporosis than vitamin-D and calcium alone.

Keywords: Glucocorticoid-induced osteoporosis; Autoimmune disease; Bisphosphonate; Calcium; Vitamin D

Introduction

Since Harvey Cushing first noted the coexistence of excess cortisol and loss of skeletal mass more than 70 years ago,[1] it has been shown that supra-physiological doses of corticosteroids cause clinically significant bone loss. Because of the rarity of cushing syndrome, corticosteroid -induced bone loss did not become a serious concern until these agents began to be used widely for the treatment of certain diseases. Currently, high-dose oral corticosteroids are used to treat people with a variety of medical conditions, including rheumatic diseases (e.g. rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus and vasculitis) and other medical conditions.[2-4] Corticosteroid-induced osteoporosis is the most frequent complication of long–term corticosteroid therapy, and the most frequent cause of secondary osteoporosis.[5,6] High dose glucocorticoid therapy is often necessary for the treatment of systemic autoimmune diseases. The importance of severe bone loss and prevention of secondary osteoporosis has yet to be established. We studied the effects of concomitant use of Alendronate, a bisphosphonate available in Iran, on patients with normal bone density commencing high-dose glucocorticoid therapy for the prevention of glucocorticoid-induced osteoporosis and compared it with traditional calcium and vitamin D therapy. The results show that Alendronate could prevent the bone loss induced by high doses of glucocorticoids in patients with systemic autoimmune disease.[7] Moreover, it focuses on the mechanisms of oral glucocorticoid-induced osteoporosis in autoimmune diseases and outlines prevention and treatment methods. Trabecular bone loss

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occurs early in the course of corticosteroid therapy, although both trabecular and cortical loss occur over time. Early changes in BMD can be detected in the lumbar spine and femoral neck, using dual energy x-ray absorptiometry (DXA). Bone loss is greater in the first 6 months of therapy. Bone loss continues over time and seems to be related to the dose of corticosteroid.[8] BMD measurements have been used to assess the risk of fractures in corticosteroid-treated patients. Although these measurements are accurate and precise, they may underestimate the fracture risk in patients receiving corticosteroids. When corticosteroids are administered, bone strength may not be related to bone mass as directly as it is in primary osteoporosis. For instance, in postmenopausal women, a decrease in BMD of one standard deviation is associated with a twofold increase in fracture risk.[9] The incremental increase in fracture risk may be greater in patients who are treated with corticosteroids. Therefore, BMD should be used initially and periodically to diagnose and evaluate the progress of bone loss in patients who are on corticosteroid for a long time.[7]

Materials and Methods

This prospective clinical trial was performed in Rheumatology Department of Ghaem Medical Centre in collaboration with Endocrinology and Metabolism Research Center. Of 250 outpatients who had an autoimmune disease such as SLE, Polymyositis, or Dermatomyositis and had been visited in rheumatology wards and clinics of Ghaem Hospital affiliated to Mashhad University of Medical Sciences (MUMS), 100 agreed to undergo the proposed treatment plan. These patients had either normal BMD or were in the range to be considered as osteopenia. It was necessary to use a high dose of glucocorticoid (30-80 mg/day). Due to BMD-reduction side-effect of this drug, a preventive measure was required to be taken. Seventy two patients completed the treatment. The other 28 patients either did not follow the course or we had to make some changes in their treatment plan and consequently they were excluded from this study. Of 72 patients included, 65 were women and 7 adult men with a mean age of 36.6 years. These patients were randomised into 2 equal groups. Group 1 (n=36) received oral vitamin D, 50000 IU, twice weekly and calcium, 500 mg, twice a day. Group 2 (n=36) received oral vitamin D, 50000 IU, twice weekly, calcium, 500 mg, twice a day, and alendronate, 10 mg/day. Both groups took a high-dose (30–80 mg/day) of glucocorticoid, which was gradually (1-1.5 years) reduced. No placebo was administered to any of the patients in the two groups. The treatment period lasted 18 months. During the course of the treatment, the patients were regularly visited to ensure if they complied with our prerequisite requirements and had not developed any complications. Initially, a BMD test of the lumbar spine (L2-L4) and femoral neck was performed for all patients, using a DEXA device (Lunar DPX-1Q, Medison, W1 USA) with an accuracy of 0.001 gr/cm^2. We also evaluated the presence of any vertebral fractures using radiography. A BMD test of each patient for both the lumbar spine (L2-L4) and femoral neck was performed . For each area (i.e. lumbar spine (L2-L4) and femoral neck), a statistical test was performed to compare the BMD reduction Considering a p value less than 0.05 as significant, it was found that the two variances were equal for both areas. Second, for each one, the mean of the two samples was compared, using t-test. The hypothesis that the two means were equal was rejected for both areas. Therefore, it was concluded that the decrease in mean BMD of group 1 was higher than that of group 2. At the end of the study, the treatment of both groups continued with vitamin D, calcium, and alendronate.

Results

Seventy two patients with autoimmune disease undergoing glucocorticoid therapy were divided into two groups. Group 1 was treated with oral vitamin D, 50000 IU, twice weekly and calcium, 500 mg, twice daily. Group 2, on the other hand, was treated with oral vitamin D, 50000 IU, twice weekly; calcium, 500 mg, twice daily; and alendronate, 10 mg per day, for 18 months. The patients were followed clinically undergoing densitometry and X-ray of the lumbar spine and hip area. It was noticed that by the end of our study period, a decrease in lumbar spine BMD occurred by -1.67% in group 1 as compared to the beginning of the study. On the other hand, lumbar spine BMD increased by +2.4% in group 2. The results showed that bone loss in the lumbar spine in group 1 was noticeable while in group 2 there was no bone loss and even there was an improvement in BMD. BMD in the femoral neck also decreased in group 1 by -2.1% while it increased in group 2 by +1.8%. Radiography revealed that one patient from group 1

developed hip fracture. None of the patients developed vertebral fracture in either group 1 or 2.

Discussion

Substantial data in the literature support the use of bisphosphonates in corticosteroid-induced osteoporosis. Indeed, in a recent analysis assessing calcitonin, vitamin D, fluoride, and bisphonates in corticosteroid-treated patients, bisphosphonate had a greater bone density supporting effect.[10] Thus, the preventive therapy using bisphosphonates should be considered when commencing high-dose glucocorticoid therapy even in those with normal bone density. We found that alendronate significantly increased the lumbar-spine and hip density in patients receiving glucocorticoid therapy. Fractures and bone loss are common in those receiving corticosteroids. Since elderly patients are treated with corticosteroids for a variety of illnesses, the prevalence of corticosteroid-induced osteoporosis, fractures, and associated morbidity and mortality can increase unless an aggressive intervention is undertaken. This starts with the patient's awareness and education about the risks and benefits of corticosteroid therapy and the need to prevent the devastating fractures caused by corticosteroids. Ideally, corticosteroid therapy should be discontinued as soon as possible. When administration of corticosteroids is required, one would hope to be able to prevent fracture, using agents diminishing the fracture risk. Bisphosphonates as potent bone resorption inhibitors have been shown to reduce bone mineral density and vertebral fractures rate. Therefore, they appear to be the first choice in the prevention of corticosteroid-induced osteoporosis.[11]

Patients at particular risk for osteoporotic fractures include postmenopausal women, those with a history of previous fracture or a family history of hip fracture, and those with a low bone density at disease onset. In these individuals, it may be possible to reduce the risk of fractures, using the least effective corticosteroid dose and preventive agents such as bisphosphonates when corticosteroids are administered. Meanwhile, bisphosphonates remain the treatment of choice.[3,4] Hormone replacement therapy, calcitonics, and vitamin D are valuable adjuncts to the bisphosphonates. Adequate intake of calcium and an exercise program might also be beneficial but should be used in conjunction with other therapies.[12]

In Fig. 1, we have compared our results with those of Saag's study,[13] for the same bisphosphonate, i.e. Alendronate. The BMD change patterns seem to be similar in both studies, despite two major differences namely the geographic location of patients and the average patients' age (36.6 in our study and 56 in Saag's). The age difference in the two studies becomes significant, noticing that in our study all the women were premenopausal while almost two thirds were postmenopausal in Saag's.

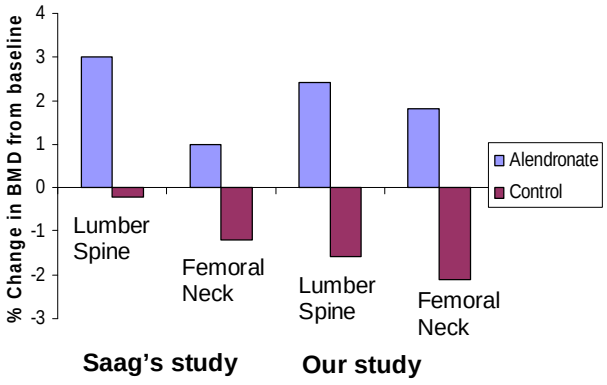

Fig 1: Comparison of our results with Saag's study[13] for BMD changes

In conclusion, these findings imply that the use of Alendronate can prevent bone loss induced by high-dose glucocorticoid in the premenopausal women and middle-aged men with systemic autoimmune diseases such as SLE. The first choice for prevention of corticosteroid-induced osteoporosis is bisphosphanates, e.g. alendronate.

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