An Evaluation of Managing and Educating Patients on the Risk of Glucocorticoid-Induced Osteoporosis

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ABSTRACT

Objective: To assess the impact of risk management activities on patient risk of glucocorticoid-induced osteoporosis.

Methods: Ninety-six adult patients taking chronic glucocorticoid therapy in 15 community pharmacies. Patients in the control group received usual and customary care. Patients in the treatment pharmacies received education and an educational pamphlet about the risks of glucocorticoid-induced osteoporosis. In addition, the treatment group pharmacists monitored the patients' drug therapy, to identify and address drug-related problems. Data including the glucocorticoid taken by the patient, medications, and osteoporosis risk factors were collected at baseline and after 9 months of monitoring, via Web-based survey completed in the pharmacy. Using an intent to treat approach, the pre–post frequency changes were compared with contrasts for presence of bisphosphonate therapy, presence of estrogen therapy, presence of calcium supplement, discussion of glucocorticoid-induced osteoporosis risk, discussion of bone density test, presence of bone mineral density test, reported inactivity, and reported low calcium diet.

Results: The contrast was significant in favor of the treatment pharmacies for the frequency of patients taking a calcium supplement (Control [–6.9%] vs. Treatment [17.1%], $P < 0.05$). No other contrast was significant.

Conclusions: Community pharmacists are capable of increasing calcium supplementation among patients at risk for glucocorticoid-induced osteoporosis. Pharmacists who educate at-risk patients can impact the self-care of these patients.

Keywords: glucocorticoid, osteoporosis, pharmacist, steroid.

Introduction

The chronic use of glucocorticoids is commonly employed in the treatment of patients who have chronic inflammatory conditions such as persistent asthma, rheumatoid arthritis, and inflammatory bowel disease. It has been estimated that more than one million people in the United States receive long-term glucocorticoid therapy [1]. Patients who are on long-term glucocorticoid therapy are at risk for osteoporosis and fractures [2–11] The adverse effect of glucocorticoids on bone is most rapid during the first 6 months of therapy and seems to be dose dependent with doses ≥7.5 mg/day increasing the patient risk, though even low doses of chronic prednisone therapy can put a patient at potential risk [12,13]. There are several strategies that clinicians can use to prevent and treat glucocorticoid-induced osteoporosis including appropriate monitoring, instructing patients about dietary and lifestyle changes, and therapeutic management [14–25]. Unfortunately, although guidelines have been published, many patients still do not receive appropriate prophylaxis for glucocorticoid-induced osteoporosis, such as calcium supplementation [26–28].

Community pharmacists are in an ideal position to screen and identify patients at risk for osteoporosis [29–31]. Specifically, community pharmacists interact regularly with patients and physicians and can initiate a management process that can reduce the risk of glucocorticoid-induced osteoporosis. By communicating with physicians, educating patients, and providing appropriate monitoring services, community pharmacists can improve medication use for patients on long-term glucocorticoid therapy. Given the need for action and the potential benefit offered by community pharmacists, the goal

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of this project was to utilize a network of pharmacists specifically trained to reduce the risk of patients on chronic glucocorticoids. The objective for this study was to assess the impact of pharmacists' risk management activities on patient risk of glucocorticoid-induced osteoporosis.

Risk Factors for Glucocorticoid-Induced Osteoporosis

There are several risk factors associated with glucocorticoid-induced osteoporosis with the dose and duration of the steroid being a major contributor to bone loss [32–37]. As mentioned previously, the most rapid bone loss in patients taking systemic corticosteroids occurs in the first 6 to 12 months of therapy with estimates of up to 10% to 20% overall loss of bone mass [3]. The mechanisms by which the corticosteroids affect bone include decreasing the intestinal absorption of calcium and phosphate, increasing urinary calcium excretion, inducing a secondary hyperparathyroidism, reducing circulating estrogen and testosterone, and inhibiting osteoblast proliferation and function [5]. More recent information emphasizes the adverse effect that chronic corticosteroid therapy has on osteoblastic activity which results in a reduction in bone formation and a decrease in the ability of bone tissue to repair itself. More specifically, chronic glucocorticoid use may cause an increase in the apotosis of osteoblasts and osteocytes and suppress the production of new osteoblasts and osteoclasts [38,39]. Daily doses greater than or equal to 7.5 mg of predisone or it's equivalent appear to cause greater loss of bone compared to lower steroid doses with trabecular bone being more affected than cortical bone [3,16].

In general, risk factors for osteoporosis include cigarette smoking, excessive alcohol consumption, sedentary lifestyle, and hypogonadism. These factors may further increase an individual's risk of glucocorticoid-induced osteoporosis. In addition, individuals who have a lower baseline bone mineral density and/or who take medications that are associated with secondary causes of bone loss (e.g., thyroid hormone, anticonvulsants) are more susceptible to glucocorticoid-induced osteoporosis. Also, if the individuals who are taking systemic corticosteroids have an inadequate calcium and vitamin D intake they may be more susceptible to bone loss [3,6,13,16]. Lastly, unlike the other common risk factors associated with osteoporosis including age, ethnicity, and sex; these factors have not been associated with glucocorticoid-induced osteoporosis [4,11]. In other words, any individual who initiates a systemic corticosteroid (≥7.5 mg/day) is at risk of glucococorticoid-induced osteoporosis regardless of their age, sex, or ethnic background. Nevertheless, these factors should be considered because older postmenopausal women of Caucasian or Asian decent have a greater risk for the fact that they may have a lower bone mass when they initiate the corticosteroid [3].

Methods

Selection of Pharmacies

This study used a randomized control design in which 15 community pharmacies were randomized to treatment (n = 8) or control (n = 7). Participating pharmacies are in a network of pharmacies that are members of Outcomes Pharmaceutical Health Care®, a specialized provider network. The Outcomes pharmacies are a diverse set of community pharmacies, including independent pharmacies and retail chains. A subset of these pharmacies in eastern Iowa has received training and/or certification in monitoring drug therapy and participating in research projects The pharmacies participating in this study are located in communities ranging from less than 2000 to more than 100,000. The number of pharmacies in the communities ranged from 1 to 38. There were a total of 100 pharmacies in the communities in which the 15 pharmacies are located. This indicates that some of the pharmacies were the only pharmacy providers in their communities while others were in a highly competitive environment. Some pharmacies are located within a clinic, while others are freestanding businesses.

All pharmacists participating in the study received approximately 4 hours of classroom education/training on the pathophysiology and management of glucocorticoid-induced osteoporosis. In addition, they were given a packet of articles for independent study, to which they could refer if they had further questions regarding prevention and treatment strategies of glucocorticoid-induced osteoporosis. Participation of the Outcomes pharmacies was contingent on all pharmacists receiving the training.

Study Design

In all pharmacies, patients 18 years of age or older who had been on the equivalent of at least 7.5 mg of prednisone for at least 6 months were identified, using prescription dispensing records. These patients were believed to be at high risk for developing osteoporosis. Patients were contacted through mail by a pharmacist in each practice and asked to participate. Those who agreed to

participate signed an informed consent form. The project was approved by the Human Subjects Committee at the University of Iowa.

Patients in the control group received usual and customary care. Patients in the treatment pharmacies received education and an educational pamphlet about the risks of glucocorticoid-induced osteoporosis. In addition, the treatment group pharmacists monitored the patients' drug therapy, using Outcomes Encounter Program. The Encounter program uses a Web-based claims system that pays pharmacists to identify and address five types of drug-related problems: appropriateness of dose, proper regimen, potential interactions, nonadherence, and adverse effects. The initial evaluation focused on the patient's glucocorticoid therapy and any medications being used to manage the risks of developing glucocorticoid-induced osteoporosis. Subsequent reviews by the pharmacists included evaluations of drug therapy being studied in addition to other medications the patients were taking. Any problems that were identified were discussed with the patient and/or the prescribing physician. A standardized physician communication form was created and utilized by the treatment pharmacies. A letter was sent to the physicians who had patients enrolled in the treatment pharmacies explaining the program and giving them the opportunity to review the communication form that the pharmacists would be sending out to them.

Data were collected at baseline and after 9 months of monitoring, from patients via a Web-based survey completed in the pharmacy. The survey collected information about the glucocorticoid taken by the patient (drug, dose, regimen, and indication), comorbidities, other medications, and herbals. Patients also reported whether or not: anyone had discussed osteoporosis risk from glucocorticoids, anyone had discussed a bone mineral density test, and they had a bone mineral density test performed.

The survey also asked patients about specific risk factors for osteoporosis. The patients stated the presence or absence of 10 risk factors for osteoporosis: small frame, being female, Caucasian or Asian, inactivity, low calcium diet, tobacco use, alcohol consumption, being postmenopausal, a history of bone fracture, and a family history of osteoporosis [40].

Data Analysis

Frequencies were tabulated for each variable. Chi-square tests were run to compare frequencies at baseline between the groups. Also, using intent-to-treat approach, contrasts compared the difference between control group baseline and control group 9 month values with the difference between treatment group baseline and treatment group 9 month values. These variables were: presence of bisphosphonate therapy, presence of estrogen therapy, presence of calcium supplement, discussion of glucocorticoid-induced osteoporosis risk, discussion of bone density test, presence of bone mineral density test, reported inactivity, and reported low calcium diet.

Results

Ninety-six patients were enrolled (70 treatment, 26 control). Eighty patients completed the study (61 treatment, 19 control). The majority in both groups were taking the same corticosteroid dose daily at baseline and 9 months (Table 1). The frequencies for corticosteroid doses within and between the two groups did not change significantly between baseline and 9 months. The diagnoses for the use of the corticosteroids included: chronic obstructive pulmonary disease (COPD), asthma, rheumatoid

Table 1 Frequency (%) of reported risk factors for osteoporosis at baseline

Risk factor	Control baseline (n = 26)	Treatment baseline (n = 70)
Small frame	8 (30.8)	29 (41.4)
Female	15 (57.7)	52 (74.3)
Caucasian or Asian descent	24 (92.3)	59 (84.3)
Inactivity	13 (50)	35 (50)
Low calcium diet	8 (30.8)	24 (34.3)
Tobacco use (smoker)	6 (23.1)	10 (14.3)
Alcohol use*	8 (30.8)	5 (7.1)
Being postmenopausal*	9 (34.6)	40 (57.1)
History of fracture	3 (11.5)	21 (30)
Family history of osteoporosis	5 (19.2)	12 (17.1)
Prednisone average daily dose	(n = 20)	(n = 51)
Less than 1 mg	0 (0)	3 (5.9)
1–4 mg	1 (5)	3 (5.9)
5–9 mg	7 (35)	21 (41.2)
10–14 mg	7 (35)	18 (35.3)
15–19 mg	1 (5)	1 (2)
20–29 mg	3 (15)	3 (5.9)
More than 30 mg	1 (5)	2 (3.8)
Length of treatment with corticosteroid	(n = 24)	(n = 62)
Less than 1 years	4 (16.7)	5 (8.1)
1–2 years	3 (12.5)	15 (24.2)
3–5 years	7 (29.1)	12 (19.3)
6–10 years	6 (25)	15 (24.2)
More than 10 years	4 (16.7)	15 (24.2)
Mean (SD) number of medications	5.58 (3.10)	7.04 (3.16)

*Chi-square significant for comparison of baseline characteristics between groups at *P* < 0.05.

Table 2 Frequency (%) of modifiable risk factors at baseline and 9 months

	Control baseline (n = 26)	Control 9 months (n = 19)	Treatment baseline (n = 70)	Treatment 9 months (n = 61)
Inactivity	13 (50)	7 (36.8)	35 (50)	24 (39.3)
Low calcium diet	8 (30.8)	3 (15.8)	24 (34.3)	11 (18)[†]
Tobacco use (smoker)	6 (23.1)	3 (15.8)	10 (14.3)	8 (13.1)
Alcohol use*	8 (30.8)	4 (21.1)	5 (7.1)	7 (11.5)

*Chi-square significant for comparison of baseline characteristics between groups at $P < 0.05$.
[†]Chi-square significant for comparison of baseline and 9 months within group at $P < 0.05$.

arthritis, polymyalgia, colitis, Addison's disease, Crohn's disease, cancer, lupus, multiple sclerosis, vasculitis, and polymyositis.

Also, of the frequencies of reported risk factors for osteoporosis (small frame, sex, race, inactivity, low calcium diet, tobacco and alcohol use, post-menopause, history of fracture, family history) only alcohol use and postmenopause were different between the groups (Table 1). There was a significant decrease in the frequency of patients reporting that they were on a low calcium diet within the treatment group (Table 2).

At baseline, the reported presence of bisphosphonate was higher in the treatment group than in the control group. The treatment group showed a significant change between baseline and 9 months for the addition of bisphosphonate, estrogen, and/or the addition of calcium supplementation (Table 3). Contrasts comparing the change in frequencies between the groups showed a significant difference in the change only for the presence of a calcium supplement. The treatment group had a significant increase in the number of patients who had started on a calcium supplement, compared to the change in the control group.

The frequency of discussion of glucocorticoid-induced osteoporosis risk between the pharmacist and the patient did increase significantly in the treatment group from baseline, although the change was not significant when contrasting the change between the two groups. Similarly, the patient's awareness of a test to measure bone mineral density increased in the treatment group, although it was trending upward for the control group and the change between groups was not significant. Lastly, both groups demonstrated an increase in the frequency of patients who reported that they had a bone density test performed, although the change was not significant between the groups (Table 4).

Table 3 Frequency (%) of presence of therapy

	Control baseline (n = 26)	Control 9 months (n = 19)	Treatment baseline (n = 70)	Treatment 9 months (n = 61)
Bisphosphonate therapy*	0 (0.0)	2 (10.5)	12 (17.1)	16 (26.2)[†]
Estrogen therapy	0 (0.0)	0 (0.0)	9 (12.9)	10 (16.4)[†]
Calcium supplement	10 (38.5)	6 (31.6)	27 (38.6)	34 (55.7)[†,‡]

*Chi-square significant for comparison of baseline characteristics between groups at $P < 0.05$.
[†]Chi-square significant for comparison of baseline and 9 months within group at $P < 0.05$.
[‡]Contrast comparing change in control to change in treatment groups significant ($P < 0.05$).

Table 4 Frequency (%) bone density test awareness and testing

	Control baseline (n = 26)	Control 9 months (n = 19)	Treatment baseline* (n = 69)	Treatment 9 months (n = 57)
Aware of bone density test	21 (80.8)	18 (94.7)	52 (75.4)	54 (94.7)[‡]
Reported bone density test performed[†]	6 (24)	12 (63.2)[‡]	34 (52.3)	41 (71.9)[‡]

*There were only 65 usable responses for reported bone density test performed at baseline.
[†]Chi-square significant for comparison of baseline characteristics between groups at $P < 0.05$.
[‡]Chi-square significant for comparison of baseline and 9 months within group at $P < 0.05$.

Using the Encounter program, pharmacists in the treatment arm were able to identify and make recommendations on 16-drug therapy problems related to glucocorticoid-induced osteoporosis. Of these 16 problems, 6 addressed the risk of prednisone related adverse drug reactions. Seven of the identified problems recommended changing the dose or type of calcium supplement to improve therapy. Other identified drug therapy problems included issues of adherence and duplicate therapy.

Discussion

Effect on Risk Management Activities

The patients who were enrolled in the study had other risk factors for osteoporosis in addition to their glucocorticoid use. It is not surprising that the nonmodifiable risk factors (small frame, sex, race, postmenopausal, history of fracture, and family history) remained unchanged from baseline to 9 months between and within groups. Nevertheless, two of the modifiable risk factors, inactivity and low calcium diet, had a downward trend from baseline to 9 months for both groups. The decrease in frequency of reported low calcium diet was significant for the treatment group, but not for the control group. This change is not surprising given that the treatment group reported a significant increase in calcium supplementation as compared to the control group.

The treatment group had a significant increase in the frequency of patients who were started on bisphosphonates, estrogen, and calcium supplements. In addition, 44% of the pharmacist interventions focused on calcium. When the pre–post frequency changes were compared between the groups, the contrasts were significant only for the frequency of patients who are taking a calcium supplement. This means that a sizable increase occurred in the control group for presence of bisphosphonate and for presence of estrogen. One explanation for this result is that pharmacists in both groups were given comprehensive education and training in glucocorticoid-induced osteoporosis, and as members of the Outcomes® network, they had received extensive training in therapeutics and skill development. During the project training, treatment and control pharmacists were instructed on the importance of baseline testing of bone mineral density and the importance of medications and calcium supplements for treatment and prevention of osteoporosis. This training may have caused the control pharmacists to make a therapeutic intervention, resulting in the increases for bisphosphonate and estrogen in the control group. In addition, the increase in the presence of bisphosphonate therapy in both groups could have been stimulated in part by the marketing activities of the manufacturers of bisphosphonates.

The patients who went to the treatment pharmacies received an educational session about the risks of glucocorticoid-induced osteoporosis. As part of the education, they received an educational pamphlet that emphasized the importance of calcium supplementation. This combination of education by a pharmacist and written information appeared to be effective in influencing patients to take a calcium supplement. In addition, the pharmacists addressed calcium supplements in some of their Encounter services. Together, the education and monitoring raised patients' reported use of calcium supplements.

Because glucocorticoid-induced osteoporosis results in a negative calcium balance, it is important that individuals who are started on long-term systemic corticosteroid therapy begin monitoring their calcium and vitamin D intake [3,5,6]. Current guidelines recommend that patients maintain a daily calcium intake of 1500 mg/day along with 800 IU of vitamin D, unless contraindicated [12]. This simple intervention will help to normalize the calcium balance which was adversely affected by the corticosteroid. Furthermore, by restoring the calcium balance this may limit the amount of bone loss experienced by the individual. This was further emphasized in a study looking at daily calcium and vitamin D supplementation in patients taking chronic low doses of prednisone (average of 5.6 mg/day). The supplementation prevented loss of bone mineral density in the lumbar spine and trochanter in patients using chronic prednisone therapy for rheumatoid arthritis [41]. Although calcium and vitamin D supplementation is an important intervention, it is usually not enough to reduce the risk of bone loss associated with systemic corticosteroids. Most patients will need additional agents such as bisphosphonates to provide them with adequate protection from additional bone loss [3,5,13].

Identifying Patients at Risk for Glucocorticoid-Induced Osteoporosis

Through examination of their patient records (e.g., dispensing profiles), community pharmacists were able to identify patients who were taking sufficient amounts of glucocorticoids to put them at risk of glucocorticoid-induced osteoporosis. This required performing some reports using the computers and then some computations by the pharmacists. It

appears that such a risk screening process could be more widely used in community pharmacies. These patients then could be contacted about managing their risks.

In addition to the glucocorticoid identified from the dispensing records, 10 risk factors were assessed with a web-based survey completed by the patients in the pharmacies. Some of the risk factors are not modifiable (e.g., sex), while others potentially could be changed (e.g., low calcium diet, activity levels, smoking, and alcohol consumption). Further work should be done to develop interventions that can positively change the mutable risk factors.

Limitations

A limitation of this study was the low number of patients that were enrolled in the control group. It was up to the pharmacists to recruit patients. Some sites did a better job of recruiting, retaining, and following up with subjects in the project. Another explanation for the lower number in the control group may be that the control pharmacies were less committed to the project because they provided usual and customary services and had less contact with the patients compared to the treatment pharmacies.

Power for this study was low because of a lower recruitment of patients than what was expected. There were 163 potential patients that were originally identified by the participating pharmacies, but only 96 were recruited. Because of this low power, we were less able to detect significant differences.

Another limitation of this study is that the control and treatment patients differed somewhat at baseline. For example, fewer members of the treatment group reported using alcohol, but more reported being postmenopausal. These differences make it difficult to assess a change between the groups. To address this limitation, contrasts were used to compare changes within groups.

Another limitation is that the pharmacists in both groups were educated regarding the risks of glucocorticoid-induced osteoporosis and the prevention and treatment strategies used to reduce the risks. Also, each of the 15 sites, both treatment and control pharmacies, had participated in other research projects and had been trained in monitoring drug therapies. This may explain why the differences between the treatment pharmacies and the control pharmacies were not as great as expected. We believe that the results understate the impact that a patient monitoring and education intervention could have in most community pharmacies. Future studies could assess pharmacists who have been trained versus a peer group that has not had the same educational interventions.

Additionally, the relatively low number of pharmacist Encounter interventions is a limitation of this study. While it is difficult to precisely explain why the level was low, there are a number of possible explanations. First, only recommendations accepted by a physician were included in the Encounter claims, suggesting that differences in clinical judgment between the pharmacist and physicians may have limited the number of accepted recommendations.

Also, the treatment pharmacies may have lacked sufficient capacity to provide a high volume of monitoring services. Although these pharmacies are providing new pharmacy services, they are building their service capacity gradually. Thus, the pharmacies in the treatment group may not have communicated with the subjects sufficiently to change risk factors such as taking bisphosphonate therapy. Data were not collected on the number of times the pharmacists interacted with the subjects regarding managing their risks of glucocorticoid-induced osteoporosis.

Conclusions

Community pharmacists are capable of increasing calcium supplementation among patients at risk for glucocorticoid-induced osteoporosis. Pharmacists who educate at-risk patients and communicate with physicians can impact the management of these patients, especially self-management (e.g., taking calcium supplements). Patients who are counseled by pharmacists have an increased awareness of their risk, are more aware of the need for bone mineral density testing, and are started on therapeutic agents to manage their risk. In particular, pharmacists who counsel patients and provide them with written materials can impact patient's understanding for the importance of their therapies.

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