MONITORING AND MANAGEMENT OF BONE STATUS IN PATIENTS ON CHRONIC GLUCOCORTICOID TREATMENT — THE MEDSCHEME EXPERIENCE

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Objective. Review of administrative databases to gain insight into the investigation, management and sequelae of bone disease in patients on long-term glucocorticoid treatment.

Design. Retrospective analysis of 1998 pharmaceutical and clinical claims data for ± 2 million lives administered by Medscheme. Data were extracted for members registered with the chronic medication programme as eligible for chronic glucocorticoid treatment. Those identified were subjected to further review for evidence of osteoporosis and/or hip fracture. Subgroup analysis of peri- and postmenopausal women was carried out and compared against a control group.

Main outcome measures. Osteoporosis investigation and treatment rates in males and females; frequency of hip fractures; prescribing profiles; role of underlying disease, glucocorticoid route, gender and age in development of osteoporosis.

Results. A total of 1 614 subjects (54% females) was registered for chronic glucocorticoid treatment. Osteoporosis was diagnosed in 14.1% of females and 5.9% of males across a broad age range. Hip fractures were recorded for one female and three males. The subgroup analysis showed that osteoporosis was ± 1.5 times more common in women receiving glucocorticoids than in peri- and postmenopausal controls, and that there was greater use of vitamin D and calcium supplementation and bisphosphonates in those exposed to glucocorticoids. Multivariate analysis showed overall that female gender, increasing age and oral glucocorticoids were significantly related to osteoporosis.

Conclusion. Reference to UK and US data suggests that while local practitioners are aware of the effect of glucocorticoids on bone, the level of awareness is probably suboptimal, especially with regard to male patients.

S Afr Med J 2000; **90:** 1125-1129.

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In a previous article[1] we drew attention to the apparent underdiagnosis and undertreatment of postmenopausal osteoporosis in South Africa and proposed that perimenopausal wrist fracture is being missed as a sentinel event. This certainly does not imply that every perimenopausal woman should be screened and/or placed on prophylactic treatment, and in this regard we refer to the guideline recently drafted by the multidisciplinary Osteoporosis Working Group and endorsed by the South African Medical Association.[2] The essence of the guideline is that bone density should be evaluated in women with clinical risk factors. These risk factors are related to bone mass, bone strength and falls. Following assessment of appropriate subjects, vitamin D, calcium supplementation, and hormonal or non-hormonal therapy should be prescribed according to specific criteria, and obviously only where indicated.

Included in the list of risk factors for osteoporosis is chronic glucocorticoid treatment.[2] This is of particular importance in older individuals in whom the glucocorticoid-induced bone loss is often superimposed on suboptimal nutrition, reduced muscle mass, hypogonadism, vitamin D deficiency and secondary hyperparathyroidism.[3] It has been stated that as many as 90% of long-term glucocorticoid recipients lose a significant amount of bone,[4] and in a study by Baltzan *et al.*[5] there was a twofold increase in the rate of hip fracture in elderly women. The latter study noted that this relationship between glucocorticoid treatment and hip fracture was only shown for oral glucocorticoid therapy. Reid and Harvie[6] state in their review that glucocorticoid-induced osteoporosis is associated with a minority of fractures in women, but with a majority of osteoporosis-related fractures in men, drawing attention to the need for practitioner awareness and vigilance when committing a patient to long-term treatment, irrespective of gender and/or age.

The present study was undertaken to gain insight into the investigation, management and sequelae of bone disease in patients subjected to long-term glucocorticoid treatment. As with the study done on wrist fractures, the population surveyed represented the membership of the medical schemes administered by Medscheme (± 2 million covered lives).[1]

SUBJECTS AND METHODS

The study sample was drawn from the company's Pharmaceutical Benefit Management (PBM) database, and the primary search was for medical scheme members and/or dependants who in 1998 were registered as patients requiring chronic glucocorticoid therapy (defined in terms of Medscheme's chronic medicines programme as an approved prescription for at least 3 months). Data on age, gender, and underlying disease were extracted, and the dose of inhaled and/or oral glucocorticoid was expressed in terms of

'standard' or 'high' daily dose according to conventional dosing regimens. Once recipients of chronic glucocorticoids had been identified, the group was subjected to a second review to establish which patients were also registered for treatment of osteoporosis as diagnosed by their doctor/s and reflected in an application for funding of chronic medication. Drugs used for the latter purpose were identified and recorded. It should be noted that all applications for registration of patients onto the PBM Chronic Medication Programme are submitted by the patient's doctor and subjected to critical review by PBM in terms of criteria for the specified diagnosis and medicines prescribed.

The medical scheme membership numbers of subjects identified in the primary analysis using the PBM database were also run through Medscheme's Data Warehouse to identify those members and/or dependants who had submitted claims for bone densitometry and/or hospitalisation for hip fracture in one study year, viz. 1998. The latter process did not preclude the possibility of densitometry and/or fracture having also been claimed for in previous years.

In order to assess whether investigation and treatment rates for osteoporosis in glucocorticoid-treated subjects were the same or higher than in a control population of 'standard-risk' peri- and postmenopausal women, we compared the relevant subset of glucocorticoid-treated subjects with the control sample used in our previous wrist-fracture study.[1] Any glucocorticoid recipients were removed from the control group, which otherwise included all women above 45 years of age in a large middle- and upper-income medical scheme (30 000 beneficiaries).

Categorical data were analysed using the chi-square test, while the *t*-test was used for continuous data. All analyses were performed at an alpha level of 0.05. Variables with significant intergroup differences at the bivariate level were included in the multivariate analysis. Variables were included in a stepwise method and were entered into the model at a *P*-value of 0.1 and removed at a *P*-value of 0.15.

RESULTS

The search of the PBM database for beneficiaries registered with the chronic medication programme identified 1 614 subjects (54% females, 46% males). Table I shows that males were slightly older and were less likely to be tested for or labelled as osteoporotic. It is noteworthy that three of the four hip fractures recorded in the subjects receiving glucocorticoids occurred in males; however, because of small numbers, the difference in fracture rates between males and females was not statistically significant. Certain respiratory indications for glucocorticoid treatment (emphysema or chronic obstructive airway disease) were more common in males, whereas females were more likely to suffer from arthritis and inflammatory bowel disease. Similar groups of drugs were chosen for treatment of osteoporosis, irrespective of patient gender. In terms of the relationship between specific glucocorticoid-dependent conditions and diagnosis of osteoporosis, frequency analysis showed that inflammatory bowel disease was strongly associated with bone disease, whereas asthma was relatively underrepresented in the osteoporosis group (Table II).

The comparison between 1 361 female controls regarded as at 'standard risk' for osteoporosis and 613 similarly aged females receiving glucocorticoids is summarised in Table III. The

Table I. Comparison of glucocorticoid-treated males and females

	Female ($N = 900$)	Male ($N = 714$)	*P*-value
Age (yrs ± SD)	51.0 ± 16.6	53.0 ± 18.2	0.02
Osteoporosis (%)	127 (14.1)	42 (5.9)	< 0.001
Hip fracture (%)	1 (0.1)	3 (0.4)	0.49
Densitometry (%)	32 (3.6)	8 (1.1)	0.002
Condition			
Respiratory (%)	302 (33.6)	382 (53.5)	< 0.001
Non-respiratory (%)	595 (66.1)	332 (46.5)	
Diagnosis			
Arthritis (%)	300 (32.2)	140 (19.1)	< 0.01
Asthma (%)	234 (25.0)	187 (25.5)	0.79
Emphysema (%)	72 (8.2)	154 (21.0)	< 0.01
Inflammatory bowel disease (%)	144 (15.4)	70 (9.6)	< 0.01
Dose			
Standard (%)	867 (96.3)	682 (95.5)	0.41
High (%)	33 (3.7)	32 (4.5)	
Treatment categories			
Bisphosphonates (%)	33 (25.9)	21 (28.5)	
HRT* (%)	14 (11.0)	3 (7.1)	
Supplements† (%)	69 (54.3)	24 (57.1)	0.72
Alternative therapy‡ (%)	4 (3.1)	0	
Other§ (%)	7 (5.5)	3 (7.1)	

*Hormone replacement therapy for treatment of osteoporosis (oestrogen/progesterone in females, androgens in males).
†Vitamin D, calcium.
‡Calcitriol and sodium fluoride.
§Mainly analgesics and anti-inflammatories.

Table II. Relationship between underlying disease and osteoporosis

Diagnosis*	Osteoporotic ($N = 174$)	Non-osteoporotic ($N = 1\,491$)	*P*-value
Arthritis (%)	54 (31.0)	389 (26.1)	0.16
Asthma (%)	29 (16.7)	399 (26.8)	< 0.01
Emphysema (%)	29 (16.7)	205 (13.7)	0.28
Inflammatory bowel disease (%)	36 (20.7)	181 (12.1)	< 0.01
Other (%)	26 (14.9)	317 (21.2)	0.07

*Some subjects had more than one diagnosis.

Table III. Comparison of control and glucocorticoid groups (women > 45 years)

	Control group (N = 1 361)	Glucocorticoid group (N = 613)	P-value
Age (%)	60.1 ± 9.3	62.4 ± 9.1	< 0.001
Osteoporosis (%)	175 (12.9)	108 (17.6)	0.006
Hip fracture (%)	7 (0.5)	1 (0.2)	0.45
Densitometry (%)	110 (8.0)	37 (6.0)	0.12

difference in osteoporosis rates is particularly significant because the control group consisted of predominantly white women whereas the study population included large numbers of black women in whom osteoporosis tends to be diagnosed and/or treated less (rather than more) frequently. Chi-square analysis showed that the bone density measurement rate during 1998 was similar in the two groups, while osteoporosis was diagnosed and treated more frequently in the glucocorticoid group. Hip fracture rates were not significantly different, but numbers were small. More important is the fact that all seven hip fractures in the control group occurred in women who had not been previously identified as osteoporotic, while the single hip fracture in the study group occurred in a patient on treatment for osteoporosis. Osteoporosis occurred more frequently in the glucocorticoid group (relative risk 1.45; 95% confidence interval (CI) 1.11 -1.90), and drug management differed significantly between the groups. There was greater use of bisphosphonates and vitamin D and calcium supplements in the study group and hormone replacement therapy was resorted to less often (Table IV).

Table IV. Comparison of drug utilisation in control and glucocorticoid groups (women > 45 years)

	Control group (N = 1 361)	Glucocorticoid group (N = 613)	P-value
Dose			
Standard (%)	–	601 (98.0)	–
High (%)	–	12 (2.0)	
Treatment			
Bisphosphonates(%)	10 (5.7)	29 (26.9)	< 0.01
HRT (%)	99 (56.6)	12 (0.9)	< 0.01
Supplements (%)	32 (18.3)	57 (52.8)	< 0.01
Alternative therapy (%)	5 (2.9)	3 (2.8)	0.92
Other (%)	29 (16.6)	7 (6.5)	0.16

Reverting to analysis of the total group of 1 614 glucocorticoid-treated patients, multivariate analysis was carried out with osteoporosis as the dependent variable, and age, gender, glucocorticoid dose (standard versus high) and nature of underlying disease as independent variables. The underlying diseases were broadly categorised into conditions requiring oral glucocorticoids (almost invariably non-respiratory conditions) and those that were mainly treated with inhaled preparations (respiratory conditions). Results are summarised in Table V, and indicate that female gender, increasing age and oral glucocorticoids were associated with increased risk of osteoporosis. In this study, dose (standard versus high) was not predictive of osteoporosis, possibly because few of the subjects were on long-term high-dose therapy.

Table V. Determinants of osteoporosis

	Adjusted odds ratio	95% CI	P-value
Age (yrs)			
50 - 59	1.32	0.91 - 1.92	0.14
60 - 69	2.00	1.38 - 2.91	< 0.001
70 - 79	2.51	1.66 - 3.81	< 0.001
> 80	3.66	1.97 - 6.79	< 0.001
Gender			
Female	2.92	2.00 - 4.24	< 0.001
Conditions			
Non-respiratory*	1.52	1.07 - 2.17	0.02

*Treated predominantly with oral (versus inhaled) glucocorticoids.

DISCUSSION

This review gives an indication that among South African clinicians there is an awareness of the osteoporotic consequences of chronic glucocorticoid treatment — osteoporosis is diagnosed more frequently in subjects on maintenance glucocorticoids, and Fig. 1 shows that the diagnosis is considered across the age spectrum, with 5% of treated subjects below 40 years of age. However, the question arises as to whether clinician awareness is at the appropriate level.

Zaqqa and Jackson[4] state that as many as 90% of long-term

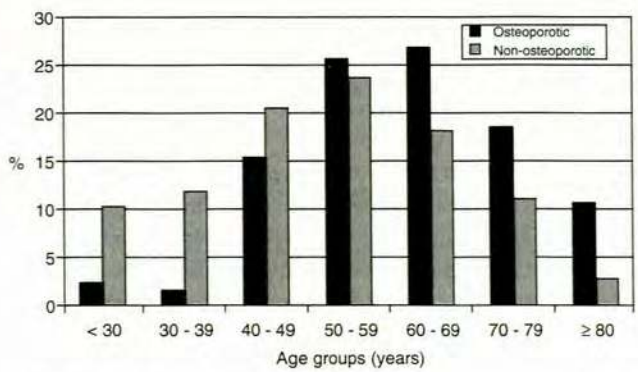

Fig. 1. Distribution of osteoporotic and non-osteoporotic subjects by age.

glucocorticoid recipients lose a significant amount of bone, and monitoring for osteoporosis is therefore essential. This view is shared by physicians at the Poole Hospital in the UK who studied 100 consecutive outpatients on glucocorticoid treatment.[7] They were concerned that only 47% of subjects were investigated, and established that 57% of those screened were diagnosed as osteoporotic, i.e. 27 of the original 100 patients. Underlying diseases in their sample were similar to those observed in the present study, with 50% of cases on treatment for arthritis and obstructive airways disease. In the study carried out by Aagard *et al.*[8] in San Francisco, 58% of 215 adult outpatients were receiving prophylaxis for glucocorticoid-induced osteoporosis. The latter studies [7,8] suggest that the 17.6% treatment rate in the present study is suboptimal, perhaps for the same reasons presented by Buckley *et al.*[9] following their survey of 425 practitioners in Virginia, USA. As appeared to be the case in our study, Virginia doctors were very aware of the deleterious effects of glucocorticoids in postmenopausal women (Table V), but they were less concerned about the effects in premenopausal women and in males. The fact that three of four hip fractures observed in our study occurred in undiagnosed and untreated males underscores the latter point.

The profile of medications prescribed for glucocorticoid-treated osteoporotic subjects is largely in keeping with current literature. Between 50% and 60% of our patients received calcium and/or vitamin D, and 25 - 30% of patients received a bisphosphonate. A recent meta-analysis has shown that vitamin D plus calcium is superior to no therapy or calcium alone in the management of glucocorticoid-induced osteoporosis, and this combination is recommended as a minimum for patients receiving long-term corticosteroids.[10] Other studies have shown alfacalcidol to be beneficial for both prevention and treatment of glucocorticoid-induced osteoporosis,[11,12] but this agent was not used to any extent in the present study. Bisphosphonates (etidronate,[13-16] pamidronate,[17] alendronate[18]) have also been studied for both primary and secondary prevention of glucocorticoid-induced osteoporosis. Fluoride,[19] calcitonin,[20] and parathyroid hormone[21] have all been studied under these clinical circumstances, but are not mainstream interventions.

It is difficult to comment on the appropriateness of treatment in this study. On the one hand, the twofold greater use of vitamin D and calcium in preference to a bisphosphonate might be appropriate, given that many cases were probably osteopenic rather than frankly osteoporotic, and prevention of osteoporosis was perhaps the objective rather than treatment of established disease. Furthermore while bisphosphonates are effective for primary prevention,[13,14,18] the cost differential (± R2 - R3.50 per day versus ± R10 per day) clearly favours vitamin D and calcium in subjects requiring long-term glucocorticoids. On the other hand, considering that in our subgroup analysis this treatment pattern applied to peri- and postmenopausal women, it is possible that hormone replacement therapy was underutilised when compared with use in the control group, particularly since glucocorticoids decrease circulating sex hormone levels, and hormone replacement should perhaps be considered unless contraindicated.

In terms of the relationship between the various underlying conditions and the development of osteoporosis, inflammatory bowel disease is usually listed as an independent risk factor for postmenopausal osteoporosis,[2] whereas with other diseases it is mainly the glucocorticoid that impacts on bone. In the present study, inflammatory bowel disease was clearly associated with osteoporosis (probably reflecting the effect of both disease and treatment), whereas asthma was underrepresented when compared with controls (Table II). The apparent lack of effect of glucocorticoids in asthma is probably due to the use of inhaled rather than oral drugs in the management of this disease.[22]

In this study of patients receiving glucocorticoids for control of a variety of diseases we found that increasing age, female gender and oral route of medication correlated with investigation of, and treatment for, osteoporosis. South African doctors who care for perimenopausal women recognise glucocorticoids as an additional risk factor for osteoporosis, and investigate and treat accordingly; however, reference to UK and US data suggests that our rate of diagnosis of glucocorticoid-induced osteoporosis across ages and gender is lower than expected.[7,8] While the primary responsibility for monitoring bone status clearly rests with the doctors who prescribe the glucocorticoid, the present study also identifies a role for the medical aid administrator and/or managed care entity. In the context of this study it would be relatively simple for a pharmaceutical benefit management system to trigger a message to medical aid members who have been approved for chronic glucocorticoid therapy, recommending that they discuss potential effects on bone with their doctors. Optimal patient care is a function of collaboration between patients, providers of service, employers and health care funders; the present study and our previous study into the relationship between wrist and hip fractures in perimenopausal women clearly show the way for the funders of the future.

The authors acknowledge the assistance of staff of PBM and Medscheme Data Warehouse in extracting the data required for this review.

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Accepted 5 Sep 2000.