# Risk factors for fragility fractures in patients with immunobullous diseases on long-term systemic glucocorticoids

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Dear Editor,

Systemic glucocorticoids remain a cornerstone of therapy in immunobullous diseases. Yet little is known about glucocorticoid induced osteoporosis (GIOP) in patients with immunobullous diseases.

We performed a retrospective review of medical records at an immunodermatology clinic in a Singaporean tertiary centre. Inclusion criteria consisted of patients with a newly diagnosed immunobullous condition between January 2011 and October 2017, who were on long-term (>= 3 months) systemic glucocorticoids at a minimum daily dose of prednisolone 15mg. Exclusion criteria included: prior treatment with systemic glucocorticoids for other indications, concurrent treatment with medications known to have effects on bone density (thyroxine, hypogonadism-inducing agents, oral contraceptives, antidepressants, antiepileptics, antipsychotics, lithium, loop diuretics, heparin, warfarin, cyclosporin), medical conditions associated with secondary osteoporosis (including rheumatoid arthritis, type I diabetes, untreated long-standing hyperthyroidism, hypogonadism, chronic malnutrition, or malabsorption and chronic liver disease). Patients without a baseline bone mineral density (BMD) study were also excluded from analysis. Data collection spanned 1 year from the time of diagnosis. Ethics committee clearance and informed consent was obtained from the study participants.

The following data were collected: patient demographics, type of immunobullous disease, date of diagnosis, systemic glucocorticoid intake including initiation and dose escalation/de-escalation, baseline BMD, use of anti-resorptive therapy and/or calcium/vitamin D supplements (equivalent to 180mg calcium and 200IU vitamin D or more) and the development of fragility fractures. We aimed to compare patients who developed new fragility fractures to those who did not.

113 patients were screened. 48 were excluded due to lack of baseline BMD, and a further 19 were excluded based on other exclusion criteria. 46 patients were included in the study (Table 1) with the following diagnoses: bullous pemphigoid (34), pemphigus vulgaris (7) and pemphigus foliaceus (5). Six (13%) patients developed a fragility fracture (4 hip, 1 patella, 1 vertebral fracture) during the 1 year of follow-up. The baseline demographics of the group who developed a fragility fracture and the group with no fracture were similar. There was no significant association between the type of immunobullous disease and development of fragility fracture rt (p=0.876). 34/40 (85.0%) of patients who did not develop a fragility fracture were on regular calcium and vitamin D supplementation, compared to only 3/6 (50.0%) of patients who developed a fragility fracture (RR=0.24). The relative risk of fragility fracture was 75% lower with the use of regular calcium and vitamin D supplementation, compared to without (RRR = 75.7%). All patients who suffered a fragility fracture were not on antiresorptive therapies – reasons for this included patient's preference, contraindications to initiation (e.g. renal failure) or when risks outweighed benefits (e.g. non-weight-bearing, immobile patients). Amongst the patients without fragility fracture, seventeen received antiresorptive therapy: 13 (32.5%) received alendronate 70mg/week, 3 (7.5%) received risedronate 35mg/week and 1 (2.5%) received denosumab 60mg 6 monthly. The use of anti-resorptive therapy was associated with reduced risk of development of fragility fracture (17/40 (42.5%) vs 0/0 (0%), p= 0.04). The average duration from initiation of systemic glucocorticoids to development of fragility fracture was 7.8mths (range from 4 to 12 months). No association was detected between mean prednisolone dose or high-dose prednisolone (>7.5mg for >=3 months) and the development of fragility fractures (Table 2). No patients were required to stop anti-resorptive therapy due to adverse

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effects. We report a positive association between the use of combination calcium and vitamin D supplementation and the reduced risk of development of fragility fracture specifically in a cohort of patients with immunobullous diseases. A Cochrane meta-analysis on the use of combination calcium and vitamin D supplementation for GIOP in a wide range of disease (not including immunobullous diseases) demonstrated a statistically significant prevention of bone loss at the lumbar spine and forearm compared to calcium alone or placebo.[1] Another Cochrane systematic review on the use of bisphosphonates for GIOP, similarly in a wide range of diseases not including immunobullous diseases, detected an absolute increase in BMD between treatment and placebo groups of 3.5% at the lumbar spine and 2.06% at femoral neck after 12 months of treatment [2] Tee et al.[3] detected a significant increase in BMD at both the lumbar spine and femoral neck in patients with newly diagnosed immunobullous disease receiving oral alendronate (10 mg/day) compared to placebo. Our findings of an association between use of anti-resorptive therapy and reduced risk of development of fragility fracture (p=0.04) are concordant and inform beyond changes in BMD values to actual clinical outcomes (fragility fracture).

The limitations of our study include the focus on a single centre and the small sample size, especially of those who developed a fragility fracture. An advantage is the analysis of management in routine clinical practice specific to patients with immunobullous diseases, in addition to the evaluation of clinical outcomes instead of radiological parameters. The "2017 American college of Rheumatology" (ACR) guidelines [4] recommend that all adults taking prednisolone at a dose of ≥2.5 mg/day for ≥3 months should optimise calcium and vitamin D intake, together with lifestyle modifications. Its low toxicity, inexpensive cost and ready availability even in a primary care setting make it even more suitable as routine prophylactic therapy. Bisphosphonates should be started in post-menopausal women and men ≥50 years of age who have moderate to high risk of fracture. Bisphosphonates are generally safe and well tolerated with severe complications such as osteonecrosis of the jaw and atypical femur fractures being rare.[5,6]

In conclusion, we identified non-usage of anti-resorptive therapy and calcium and vitamin D supplementation, respectively, as risk factors for developing fragility fractures in patients with immunobullous diseases on long term systemic glucocorticoids. The importance of these pharmacological interventions in the prevention and management of GIOP in this patient group is reinforced.

**Table 1.** Baseline demographics of study patients.

| Variable | Fragility fracture (n=6) | No fracture (n=40) |
|---|---|---|
| Sex, No. (%) | | |
| Male | 2 (33.3%) | 15 (37.5%) |
| Female | 4 (66.7%) | 25 (62.5%) |
| Age, mean (SD) | 72.2 (16.0) | 69.8 (14.1) |
| Ethnicity, No. (%) | | |
| Chinese | 4 (66.7%) | 29 (72.5%) |
| Malay | 2 (33.3%) | 3 (7.5%) |
| Indian | 0 (0.0%) | 5 (12.5%) |
| Others | 0 (0.0%) | 3 (7.5%) |

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**Table 2.** Clinical characteristics of patients who suffered a fragility fracture versus those who did not.

| Variable | Fragility fracture (n=6) | No fracture (n=40) | p |
|---|---|---|---|
| Mean daily prednisolone dose, mg (SD) | 14.85 (7.1) | 14.32 (6.2) | 0.84 |
| High-dose prednisolone (>7.5mg) for ≥ 3 months, No. (%) | 4 (66.7%) | 34 (85.0%) | 0.28 |
| Antiresorptive therapy, No. (%) | 0 (0.0%) | 17 (42.5%) | |
| Alendronate, 70 mg/week | | 13 (32.5%) | 0.04 |
| Risedronate, 35 mg/week | | 3 (7.5%) | |
| Denosumab, 60 mg 6mthly | | 1 (2.5%) | |
| Calcium/vitamin D supplementation*, No (%) | 3 (50.0%) | 34 (85.0%) | 0.04 |
| Baseline BMD (NOF) | | | |
| Normal (T score >-1.0) | 5 (83.3%) | 12 (30%) | 0.03 |
| Abnormal (T score<-1.0) | 1 (16.7%) | 28 (70%) | |